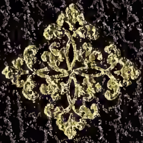
Neonatal Respiratory Adaptation



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Neonatal Respiratory Adaptation

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Preface

The purpose of this conference is to discuss what is known and what is *not known* about neonatal respiratory adaptation. The physiological and biochemical events which take place during the process of adaptation to extrauterine life are doubtless the most demanding a human being ever has to make. In consequence, a large portion of neonatal mortality and morbidity comes as the result of the failure of the newly born infant to adapt successfully to an extrauterine environment.

The problem of respiratory adaptation, whether successful or not, is exceedingly complex. As a result, this conference has attracted the interest of individuals in rather diverse fields of biology, most of which are represented here today. Our plan of attack is to begin in the uterus (indeed, a bit higher up to briefly discuss fertilization, then implantation) and discuss biological phenomena on both sides of the placenta—as well as the placenta itself. We will then come to the infant and approach the problem of its adaptation from a variety of aspects.

Our emphasis will be on new information rather than on older data. It is our hope that at the conclusion of the conference we will have asked more questions than we have answered.

THOMAS K. OLIVER, JR., M.D.,
Scientific Editor.
ROBERT H. ALWAY, M.D.,
Conference Chairman.

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Intrauterine Events and Their Effects on the Fetus

RAMSEY. We regard intrauterine life quite differently today than did our predecessors. We no longer look upon it as the ancients did, as a period of waiting to be born. We don't even think of it in the somewhat more modern light, as a period exclusively devoted to the development and elaboration of organs which can be used after birth. It is our opinion that intrauterine life is merely one phase of the long, continuous stream of the individual's total life. This was expressed most succinctly by the late Dr. George L. Streeter, who, in the introduction to *Horizons,* said, "Embryos not only develop, but they must also live." He amplified this by pointing out that the life functions, requisite for any given biological level of uterine development, must be carried on efficiently at the same time that simple organs are undergoing alteration into the more elaborate forms which can be used in extrauterine life.

In a very broad and general way, we can see that there are two means by which the given goals are attained: first, by the internal constitution of the embryo, including in this the placenta; and, secondly, through the maternal capacity to supply sustenance for life and building blocks for development.

For our necessarily abbreviated discussions today, I have selected four key points. They do not cover the entire field, but they are focused upon the special interests and talents of the group gathered here.

1. Earliest phases of development; blastocyst; implantation.
2. Maternal placenta and uterine environment.
3. Placental and fetal circulation.
4. Flaws and pitfalls in the course of fetal development.

IMPLANTATION*

BLANDAU. Obviously, we cannot expect to have a normal newborn baby unless embryonic attachment to the endometrium and implantation proceeds normally. I think, too, it is fair to state that we probably know less about the mechanism of embryo orientation within the uterus, attachment of the embryo to the endometrium, and the mechanism of implantation, than we do about the fully formed placenta, the fetus, or the newborn.

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Within the mammalian species, the appearance of the blastocysts, the mechanism of embryo attachment, and the distribution of the embryos *in utero*—if there are multiple embryos—are remarkably similar in many ways, and yet, there are very significant differences.

We have very little specific information concerning early human development. In my opinion, no one has seen a fertilized one-cell human ovum. I believe that the supposed fertilized or segmenting human eggs that Dr. Shettles pictures in his book *Ovum Humanum* are not truly fertilized or normally segmenting eggs, but are merely fragmenting ova. The two-cell egg that Drs. Hertig and Rock have described appears to be a normally fertilized and segmented egg, but even in this specimen we cannot know with absolute certainty whether it is a normally fertilized two-cell egg or a fragmented egg with two remarkably equal fragments. In a variety of mammals we may see numerous unfertilized, fragmented eggs which look perfectly normal but which do not have the specific sign of fertilization—the presence of a sperm flagellum within the egg cytoplasm. In the rat, mouse, hamster, guinea pig, bat, mole, pig, etc., the flagellum gets into the ooplasm and carries along with it mitochondria and other organelles which may be of some importance in the development of the egg. The role that these organelles may play in early development is as yet entirely unknown. It is not known whether the sperm tail is carried into the ooplasm at the time of sperm penetration in the human.

Sorokin. What do you mean by a fragmented egg, Dr. Blandau?

Blandau. If animals, such as the hamster and the rat, ovulate without mating, or if ovulation is induced by the injection of gonadotropins, a significant number of the unfertilized eggs recovered 48 to 72 hours after ovulation will appear to have divided into a number of fragments. These fragments may vary in size or they may be remarkably evenly divided so as to appear identical to cleaving fertilized eggs. The unfertilized egg of the hamster is particularly prone to segmentation without mitosis, and if examined 24 hours after ovulation, one may find a number of two-cell eggs in which each blastomere has a nucleus which appears very similar to that of a fertilized egg, but these eggs do not contain a fertilizing flagellum. Unless one has had considerable experience, one would assume that these unfertilized segmenting eggs were fertilized (compare figs. 1 and 2).

Fremont-Smith. Are there any *in vitro* moving pictures of fertilization of human sperm and ova?

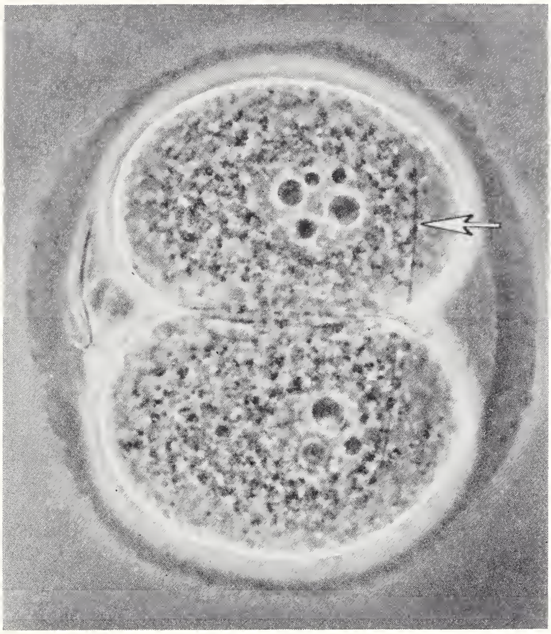

Figure 1.—Phase contrast photograph of a living two-cell rat ovum flushed from an oviduct 26 hours after fertilization. The sperm flagellum spans the two blastomeres at the arrow. An accessory sperm may be seen in the perivitelline space.

Blandau. No. *In vitro* fertilization apparently depends upon the most exacting environmental conditions. Dr. Chang* has accomplished it with rabbit and hamster eggs, but it has not yet been observed photographically. Such *in vitro* fertilized eggs were observed to segment. The segmenting eggs were inserted into the uteri of timed females, and young were born.

Fremont-Smith. Were sperm flagella inside those?

Blandau. Yes.

Pickering. You imply then that sperm mitochondria have an actual metabolic role?

Blandau. I have no evidence for this whatsoever—I am just guessing. Nonetheless, the morphological changes the mitochondria undergo are fascinating. When a spermatid is transformed into a spermatozoon, the mitochondria, which ordinarily appear rod-shaped, become globular in form and tend to arrange themselves near the periphery of the cell. Then, while the head is being transformed and compacted, and the axial filament grows out from the cell, the globular mitochondria arrange themselves in a spiral fashion around the axial filament. These globular mitochondria then fuse one with another and form a continuous spiral mitochondrial sheath which has a threadlike appearance.

---

*Dr. M. C. Chang, Worcester Foundation, Shrewsbury, Mass.

When a sperm flagellum gets into an egg, this process is reversed. The continuous thread along the axial filament again reforms into distinct globular mitochondria, and these are then distributed into the egg cytoplasm. We do not know what happens to them after they leave the spiral thread. This is an interesting problem, for the sperm flagellum brings into the egg not only nuclear material but also cytoplasmic organelles.

Many of you have seen pictures of the beautiful 5-day-old blastocyst that Hertig and Rock recovered and described. The remarkable fact here, again, is that this blastocyst appears so similar to those of most other mammals that have been studied. If I am correct, Dr. Ramsey, this human blastocyst did not have the zona pellucida around it?

RAMSEY. That's right.

BLANDAU. We don't know when the zona pellucida is lost from the human blastocyst; nor do we understand how the embryo orients itself *in utero*, so that the embryonal area is directed against the uterine epithelium.

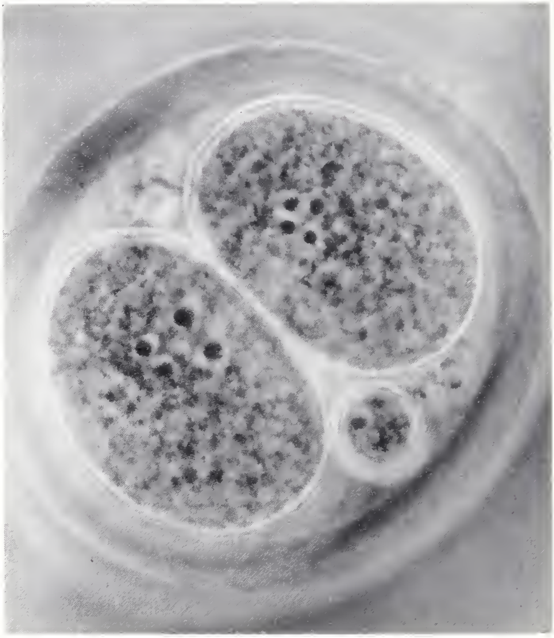

FIGURE 2.—A two-cell ovum recovered from an oviduct of an unmated female rat 28 hours after ovulation. The egg appears very similar to that shown in figure 1 but there is no sperm flagellum present. This is an unfertilized, fragmenting ovum.

The monkey blastocyst orients itself *in utero* in a manner very similar to that of the human. Mammalian blastocysts attach themselves to the uterine epithelium in a variety of ways. Teleologically speaking, it appears as if the blastocyst, which is about 125 to 150 micra in diameter, knows which is heads and which is tails. It apparently recognizes which area of the trophoblast is most suitable for initial attachment to the uterine epithelium. It is important to emphasize again that there is great species variation in the implantation process, and the phenomenon in each species must be described separately.

In most mammals, the decidual response, that is, the reaction of the endometrium to the presence of the embryo, must occur at a very precise time if implantation is to proceed normally. There are variations, however. In the human being, for example, the embryo will implant, but the decidual response will not occur until the 11th or 12th day after fertilization. Examples of species differences in implantation can be seen in the rat and guinea pig.

In the rat, if we compare the nuclei and the texture of the cytoplasm in the area immediately beneath the embryo with similar tissue at a more distant site, we note significant differences (fig. 3). In the tissues immediately subjacent to the blastocyst, the nuclei are much more rounded

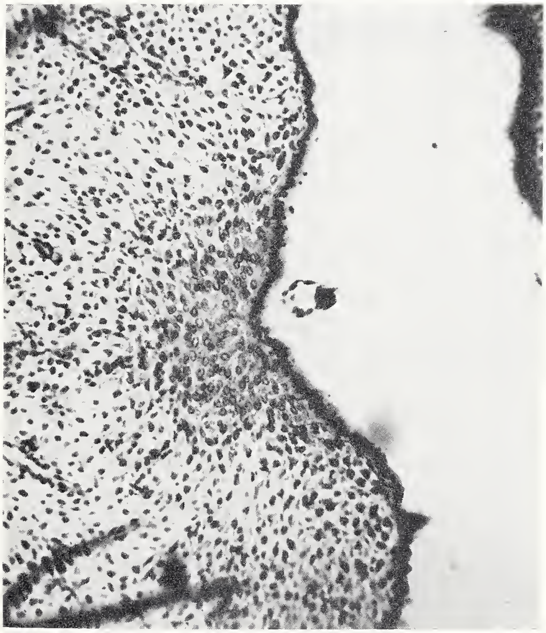

FIGURE 3.—A higher power view to show changes in the cells of the stroma immediately below the attached blastocyst.

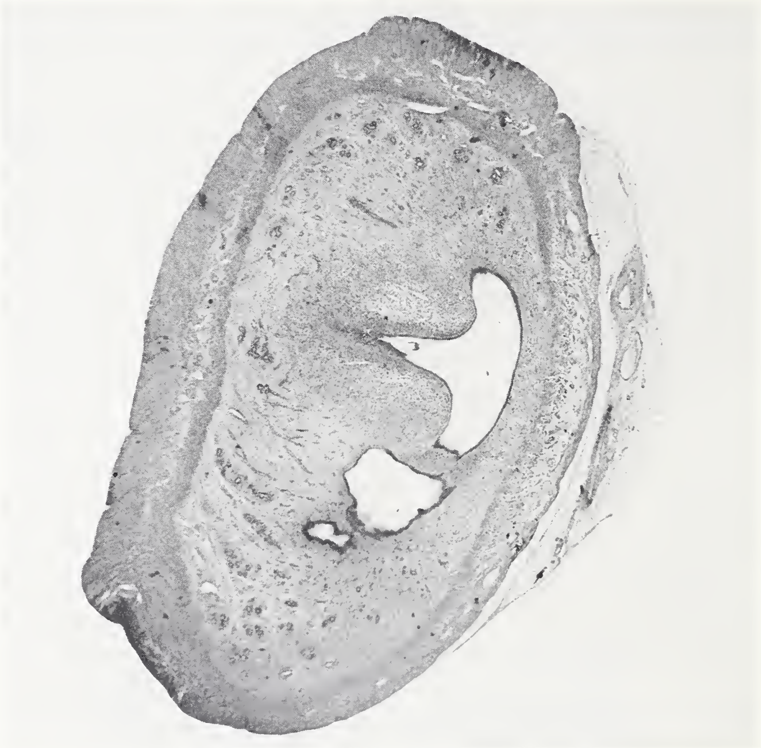

Figure 4.—A longitudinal section through a decidual response in the rat. This pregnancy is approximately 2 hours older than the one pictured in figure 3.

and the cytoplasm is stained more basophilically, indicating that there is active protein production. There is as yet no destruction of the surface epithelium of the uterus. We can conclude that the presence of the embryo has induced a change in the underlying endometrium which is proceeding at a very rapid rate. Within a few hours, the decidual response had advanced significantly (fig. 4). The fact that the superficial uterine epithelium is still intact is of particular importance; it shows no signs of injury or erosion.

Fremont-Smith. You mean there is no implantation yet? The embryo is free in the fluid of the uterine lumen?

Blandau. There is no implantation and the embryo is still free. If one opens the uterus, as one would a book, one can float the embryo from the crypt with ease by directing a tiny stream of fluid against it. The embryo is only very tenuously attached to the unbroken epithelium.

We do not know with certainty when the zona pellucida disappears from the rat blastocyst. Its disappearance is probably related to the expansion or elongation of the blastocyst shortly before attachment. We do know that the zonas are still present when the embryos drop into the cornua at the end of the third day after fertilization. We have no knowledge as to how the blastocysts, now freed from the zonas, orient themselves so that their abembryonal poles are invariably directed toward the implantation site. We do not know whether the trophoblast cells have a certain stickiness which makes them adhere to a particular site. If one removes these embryos from the cornua and rolls them about in a dish, one cannot observe any single area of stickiness when compared to another. In the rabbit, on the other hand, there is a certain amount of stickiness of the egg membranes which helps to hold the embryo in place.

After a few more hours, there is a very large increase in the decidual tissue. The growth of the endometrium has almost completely occluded the uterine lumen and the embryo now lies deeply embedded within the decidual crypt. It is only when the embryo has induced a decidual response of approximately this amount that the uterine epithelium lining the crypt will be eroded by the trophoblast cells of the embryo. When erosion begins, there is some invasion and rupture of the stromal capillaries. As a result, there is bleeding into the implantation cavity. We assume that the cells of the embryonic trophoblast cytolyze and phagocytize the uterine tissues and utilize this pabulum for the early nutrition of the embryo.

In the guinea pig, embryo attachment and implantation is quite different from that of the rat. A guinea pig embryo recovered on the sixth day after mating, just before the time of attachment and implantation (fig. 5), looks very similar to the human blastocyst except for size. The cells which comprise the inner cell mass already show some variation in size. We don't know what this means, but it may foreshadow the various groups of cells that will segregate to form the germ layers. The inner cell mass is completely surrounded by a single layer of cells which forms the limiting membrane of the trophoblast wall. This whole object is called a blastocyst. The blastocele cavity is filled with fluid, and in the living, the pressure of the fluid keeps the cells of the trophoblast pushed against the zona pellucida. At this stage of development the zona pellucida is still present.

A few hours later there is a thickening of the trophoblast membrane at the abembryonal pole. Previously, the trophoblast wall was composed of but a single layer of cells, but now the abembryonal trophoblast is composed of a number of layers of cells. One can observe a remarkable phenomenon occurring at about this time (fig. 6). The zona pellucida is intact, and the cytoplasmic projections are perforating it. The guinea pig is the only animal in which this phenomenon has been demonstrated in the living blastocyst. I am convinced, from examining preparations of implanting human and monkey embryos, that this same phenomenon may occur in living preparations of preimplanting primate blastocysts.

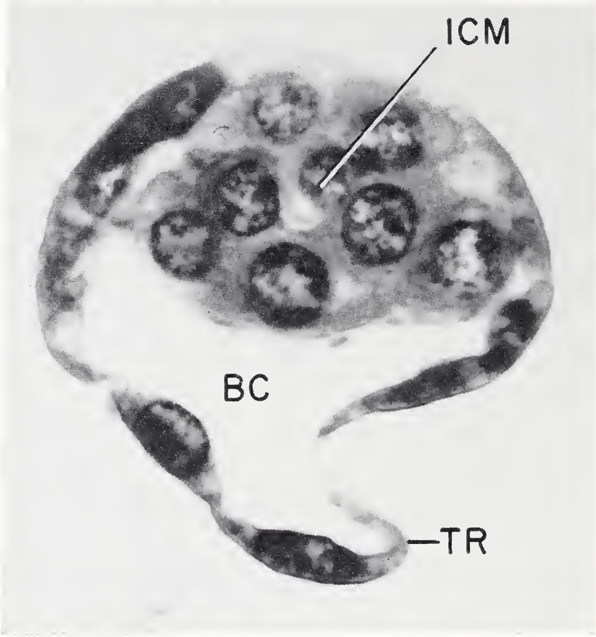

FIGURE 5.—A section through a guinea pig blastocyst recovered from the cornu 6 days after mating. ICM=inner cell mass; TR=trophoblast; BC=blastocele cavity. In this blastocyst the zona was dissolved by the acid in the fixative.

Cytoplasmic processes of the trophoblast cells continue penetrating the zona pellucida, and these extend beyond the rim of the zona pellucida. By phase microscopy and time-lapse photography, we have observed that as the trophoblastic cells lying next to the zona begin to send protoplasmic processes through the zona pellucida, these processes appear to depolymerize the resilient zonal membrane, thus forming tiny channels for the cytoplasmic projections to extend through and beyond the zona. We believe that we can see these processes secrete fluid droplets which appear as clear vesicles in the culture medium. We may speculate that these footlike processes do two things. First, they participate in orienting the embryo *in utero* so that its abembryonal pole is directed towards the uterine epithelium for proper attachment, and second, they may give off some proteolytic or cytolytic enzymes which play a role in the denudation and dissolution of the uterine epithelium and underlying stroma as the embryo invades the endometrium.

The mechanism of implantation in the guinea pig is more similar to that of the human than the monkey is to the human; therefore, in my opinion, this animal is excellent for studying the implantation phenomena.

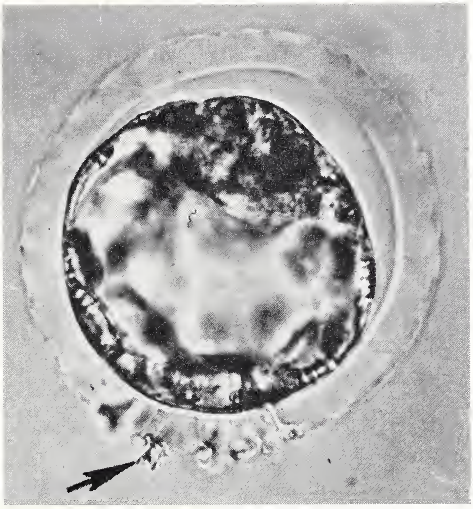

Figure 6.—A living guinea pig blastocyst recovered 6½ days after mating to show the cytoplasmic projectives (*arrow*) of the trophoblast extending through the zona pellucida at the abembryonal pole.

Fremont-Smith. This is all cytoplasm? No nuclei come through these processes?

Blandau. That is correct. Guinea pig implantation is completely interstitial. It leaves the uterine lumen and lies deeply within the stroma of the maternal endometrium.

When the zona pellucida has disappeared from the abembryonal pole, the trophoblast cells take on an entirely different appearance. They move out to form thin sheets of cells, almost syncytial in appearance. There is the rapid formation of pinocytotic vesicles along the entire edge of the cell's membrane. The nucleus and mitochondria stand out clearly. The pinocytotic vesicles move quickly toward the nucleus, where they disappear.

Approximately one-half hour after the embryo has attached to the uterine epithelium, it has completely denuded the surface (fig. 7). If one looks down upon a living, implanting embryo of this age, it appears as if the embryo had punched out a perfectly round circle of epithelial cells. Some of the trophoblast cells are invading the underlying stroma and there is some vacuolation within the stromal cells.

As the invasion of the endometrial stroma continues and implantation is finally completed, one sees a small slit in the uterine epithelium which is the implanted embryo and the implantation cavity. Implantation is now completely interstitial.

Figure 8 shows a somewhat later stage in which the inner cell mass becomes visible and the implantation process continues. The uterine

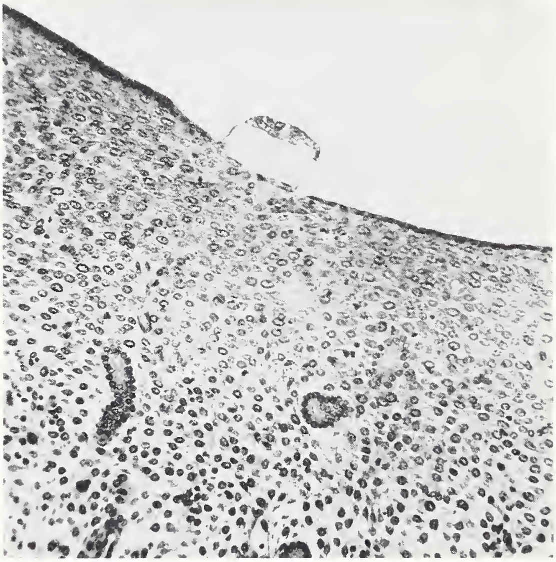

Figure 7.—A section through a guinea pig blastocyst which has completely eroded the surface epithelium. The trophoblast cells are now invading the underlying stroma.

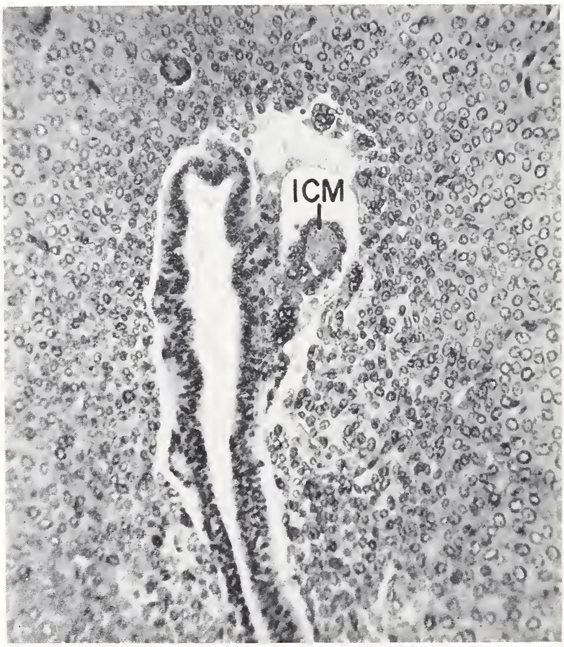

Figure 8.—Slightly older stage of implantation in which the inner cell mass of the embryo is once again clearly distinguished. ICM=inner cell mass.

epithelium has completely sealed off the embryo. The trophoblast of the embryo is actively destroying maternal tissue and enlarging the implantation cavity. By this time the decidual response is well established in the implantation area.

Figure 9 shows a section of an attaching rabbit blastocyst taken from Dr. Böving's work. The trophoblast appears to have penetrated the uterine epithelium. The early attachment of the rabbit blastocyst may occur in several places in the abembryonic hemisphere. Dr. Böving has worked out the very complex chemical interrelationships between the embryo and the endometrium at the time of attachment and invasion, and has shown how trophoblast adhesion occurs most frequently where the uterine epithelium has a capillary immediately beneath it. This, in my view, illustrates another mechanism of attachment and invasion of a mammalian embryo.

Potter. In Dr. Hartman's early pictures of the Rhesus monkey blastocyst, there was a much larger cavity in relation to the inner cell mass. Is this a species difference?

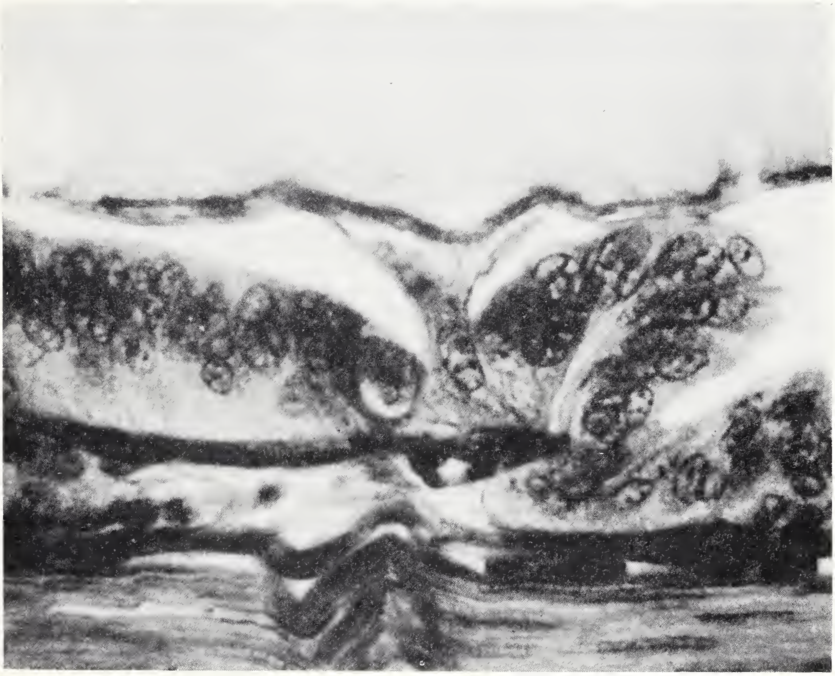

Figure 9.—Section through an attaching rabbit trophoblast. The trophoblast has penetrated the uterine epithelium and has come to lie immediately above a blood vessel. There is some evidence of cellular damage in the neighboring cells of the epithelium. Reprinted, by permission, from Böving, B. G.: Implantation. *Ann NY Acad Sci 75: 700–725 (Jan 9) 1959.*

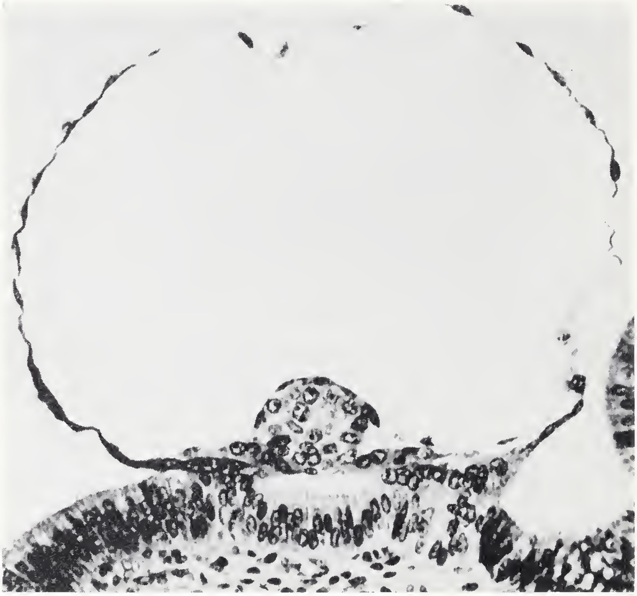

Figure 10.—A macaque blastocyst, recovered 8 to 9 days after ovulation and fertilization. Note the proliferated trophoblast cells at the abembryonal pole. The uterine epithelium shows injury; as yet there is no decidual response. Reprinted, by permission, from Heuser, C. H., and Streeter, G. L.: Development of the macaque embryo. *Contributions to Embryology 29(181): 15–55, 1941* (Carnegie Institution of Washington, publishers).

Blandau. Yes, there are species differences. The blastocysts of various animals vary greatly in size. The guinea pig blastocyst is one of the smaller, about 65 micra in diameter. The human blastocyst is about 125 micra, and the Rhesus monkey about 150 micra in diameter. But, as far as general appearance of the blastocyst is concerned, there is a remarkable similarity from species to species.

The attaching 8- to 9-day-old monkey blastocyst (fig. 10) is considerably larger, and at the time of implantation it is the embryonal pole that first invades the endometrium. There is proliferation of cells of the trophoblast wall and injury to the uterine epithelium. From what we have seen in the guinea pig, we can imagine the monkey trophoblast cells proliferating and penetrating the zona pellucida immediately before attachment. This, of course, has not been observed in the monkey but is a pertinent speculation.

EXPERIMENTAL IMPLANTATION

Blandau. It has been possible to prepare some artificial eggs and observe the decidual response. We have used beads made by adding some cobalt to ground glass and fusing them in an oxygen-gas flame, as well as beads prepared from paraffin saturated with lamp black. In contrast to the glass beads, the paraffin-saturated beads are very light. In using the paraffin beads we were thinking of the possible relationship of simple pressure of the egg to implantation. The beads are approximately 75 micra in diameter and may be injected into the oviduct at the proper time of the cycle. They will be transplanted into the cornu where they may simulate the eggs of the animal itself.

In the rat, one can induce a decidual response and effect implantation by the minutest pressure of an inert object (figs. 11, 12). If we try the same experimental procedures in the guinea pig, there is a remarkable difference (fig. 13). If one inserts artificial beads into the guinea pig uterus at the proper time of the cycle, the bead may indent the uterine epithelium slightly, but the epithelium is not eroded and there is no decidual response. However, if a bead is implanted immediately beneath the epithe-

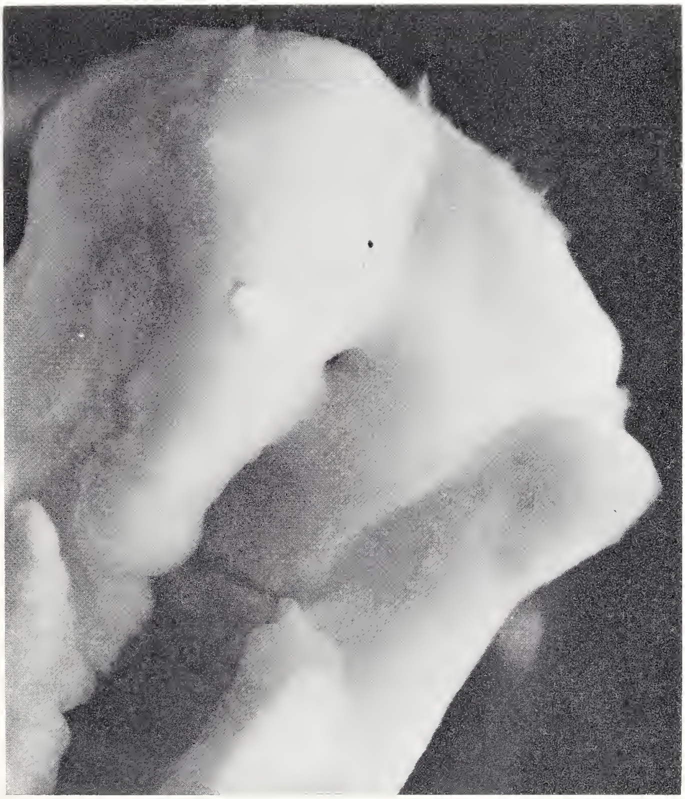

FIGURE 11.—An opened uterus (rat) showing a glass bead within the decidual crypt. A definite decidual response has occurred, identical to that induced by the embryo.

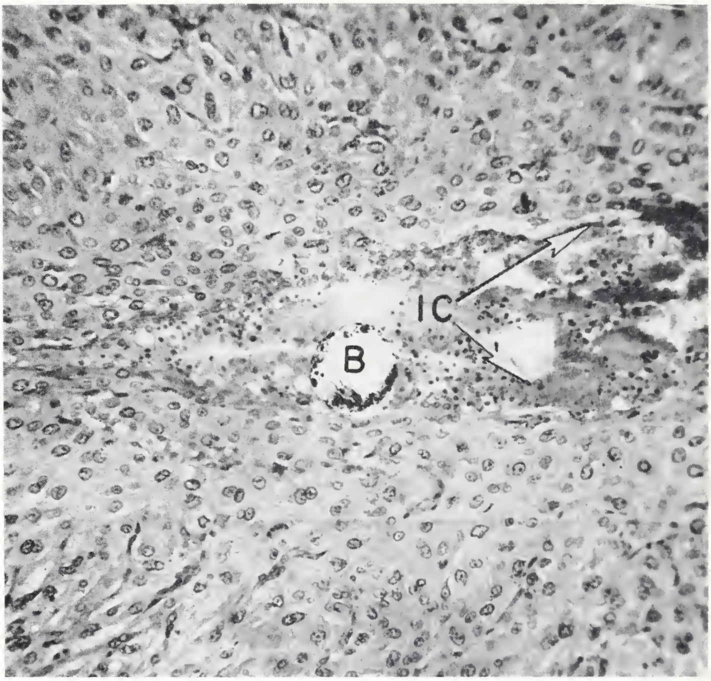

Figure 12.—Later stage in artificial implantation in which the glass bead (B) lies deeply within the decidual crypt. The uterine epithelium of the implantation crypt is completely gone, and the implantation cavity (IC) is filled with cellular debris and blood.

lium or penetrates the stroma, there is an entirely different response—one in which a decidual response has been induced (fig. 14). This occurs as a result of injury to the underlying stroma. In the rat, injury to the endometrium does not seem to be important, but in the guinea pig injury to the stroma appears to be essential.

We wish to emphasize that there are many variations from animal to animal as to the manner of embryo orientation *in utero*, embryo attachment to the uterine epithelium, induction of the decidual response, and the invasion of the stroma of the endometrium to complete implantation.

MATERNAL PLACENTA AND UTERINE CIRCULATION

Ramsey. We have been tracing the circulation from the maternal arterial bloodstream through the placenta and back into the maternal venous bloodstream in the Rhesus monkey. Our technique consists of injecting a radiopaque dye into the femoral artery of the pregnant animal. We are able to carry out successive studies during one pregnancy, and even in the same

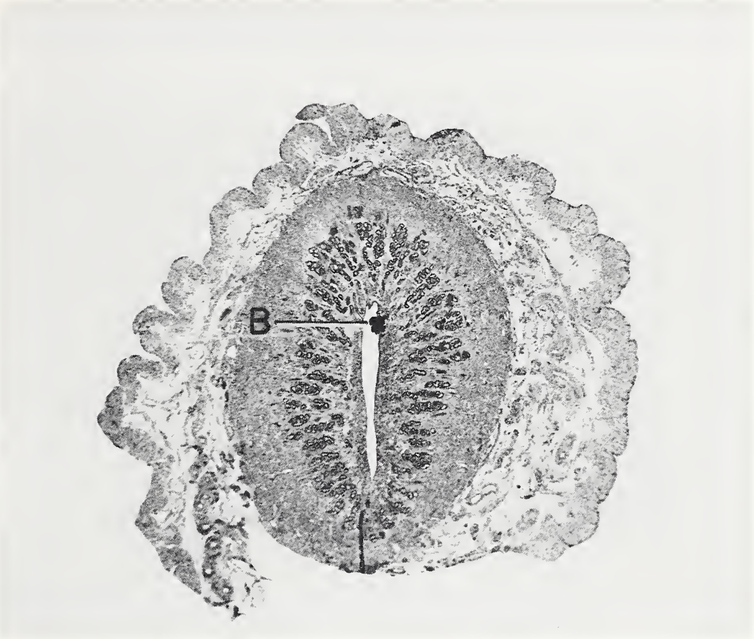

FIGURE 13.—Section of a guinea pig uterus in which glass beads were inserted into the ostium of the oviduct on the third day of the cycle and the animal killed on the eighth day. The bead (B) did not effect a decidual response.

animal in successive pregnancies. We have done this in a sufficient number of cases so that we are satisfied that the dye is nontoxic and will mimic physiologic conditions satisfactorily.

DAWES. Were the animals anesthetized?

RAMSEY. Yes. We anesthetized them with Nembutal.

The pathway of maternal blood through the placenta has been visualized by rapid serial X-rays and by cineradiography, using an image intensifier combined with a television system. Uterine activity has been simultaneously recorded by means of an intraamniotic catheter.

To study arterial inflow, a bolus of dye is injected into the femoral artery under high pressure. As shown in figure 15, the dye rises in the aorta to the renal level and returns to the pelvis under maternal arterial pressure. It fills the arteries of the uterine wall and enters the intervillous space of the placenta from the tips of the spiral arterioles in characteristic "spurts." The spurts spread and eventually coalesce.

This basic pattern varies according to whether the uterus is relaxed or contracted at the time of the injection. In the uterine contractions which occur throughout pregnancy, amplitude and frequency of contraction vary

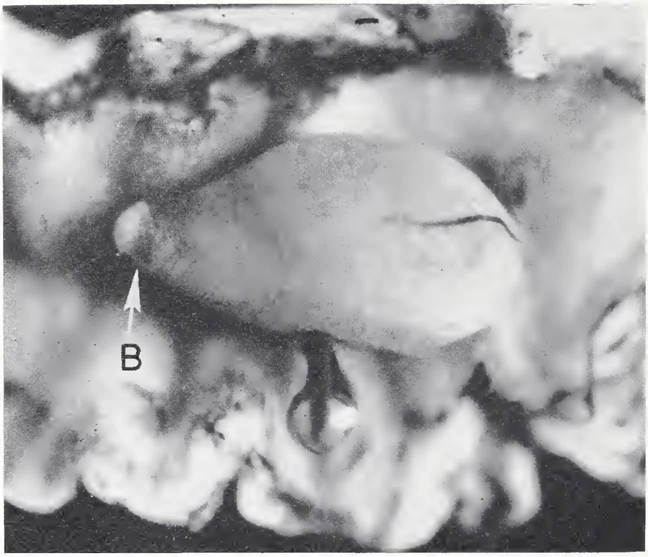

Figure 14.—Whole deciduoma within the lumen of a guinea pig uterus. The bead was inserted below the uterine epithelium on the fifth day of the cycle and the uterine cornu opened 5 days later. Note the location of the bead (B) and the large amount of decidual tissue.

with the stage of gestation (fig. 16). Strong contractions inhibit flow to the intervillous space (fig. 17). Weaker contractions impede but do not inhibit the flow (fig. 18).

To demonstrate venous outflow from the placenta, dye is injected directly into the intervillous space under low pressure. It fans out among the chorionic villi and promptly appears in the channels draining the intervillous space (fig. 19). Injections outside the intervillous space yield an unmistakably different picture from the foregoing.

Study of the effect of uterine contraction upon venous outflow has just commenced. So far it can only be said that no such dramatic effect has yet been seen as in the case of arterial inflow.

Potter. When the dye is injected into an intravillous space does it go out directly from the area injected? Does it move to the margin of the placenta or anywhere else?

Ramsey. It seems to go out very fast, if the vessels are patent.

Dawes. What was the pressure at the end of the needle?

Ramsey. This was fingertip pressure and relatively slow injection speed. We don't know the exact pressure.

There is still another aspect of the arterial circulation which deserves consideration (fig. 20). These pictures are reproduced from radiographic

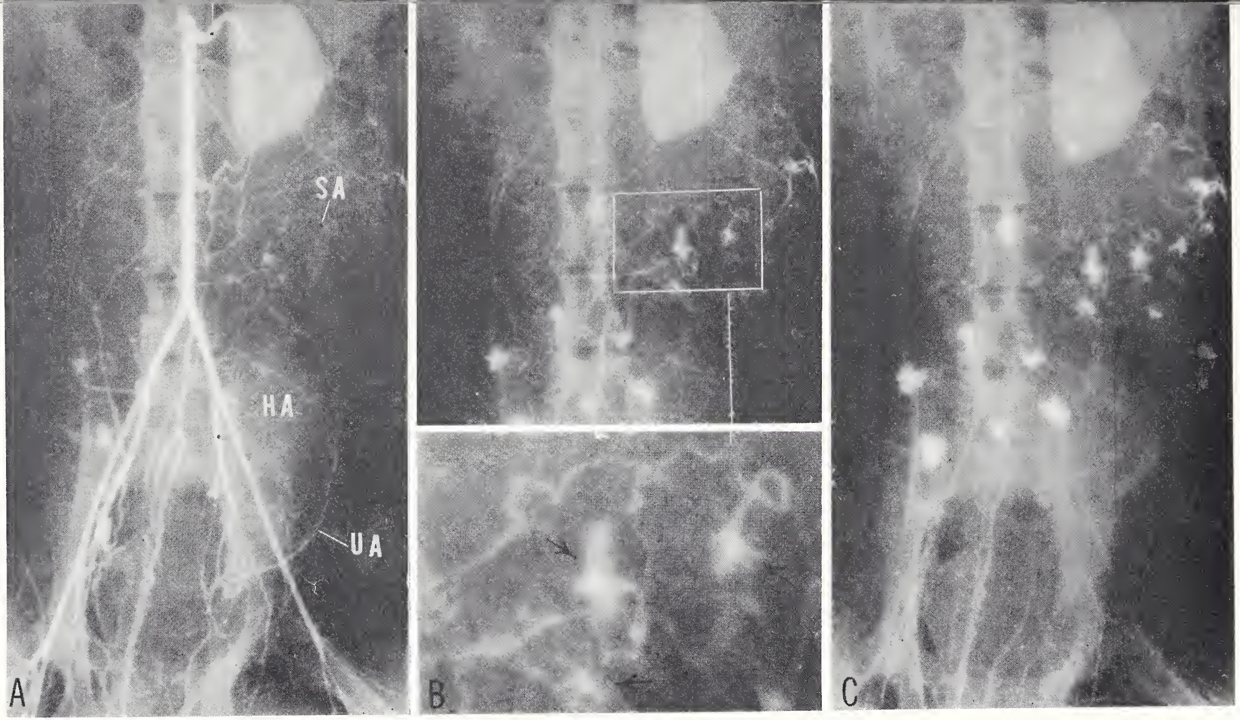

Figure 15.—Photographs of three of a series of radiograms made in a monkey (No. 12B) on the 111th day of pregnancy. *A*, made at 3½ seconds after injection of the radiopaque dye; *B*, at 5 seconds; *C*, at 6 seconds. The insert shows a magnification (× 4) of the area in the box. Arrows indicate spurts of dye into the intervillous space. RA=renal artery; SA=spiral artery of the endometrium; HA=hypogastric artery; UA=uterine artery. Reprinted, by permission, from Ramsey, E. M., Corner, G. W., Jr., Donner, M. W., and Stran, H. M.: Radioangiographic studies of circulation in the maternal placenta of the Rhesus monkey: preliminary report. *Proc Nat Acad Sci USA 46: 1003–1008, 1960.*

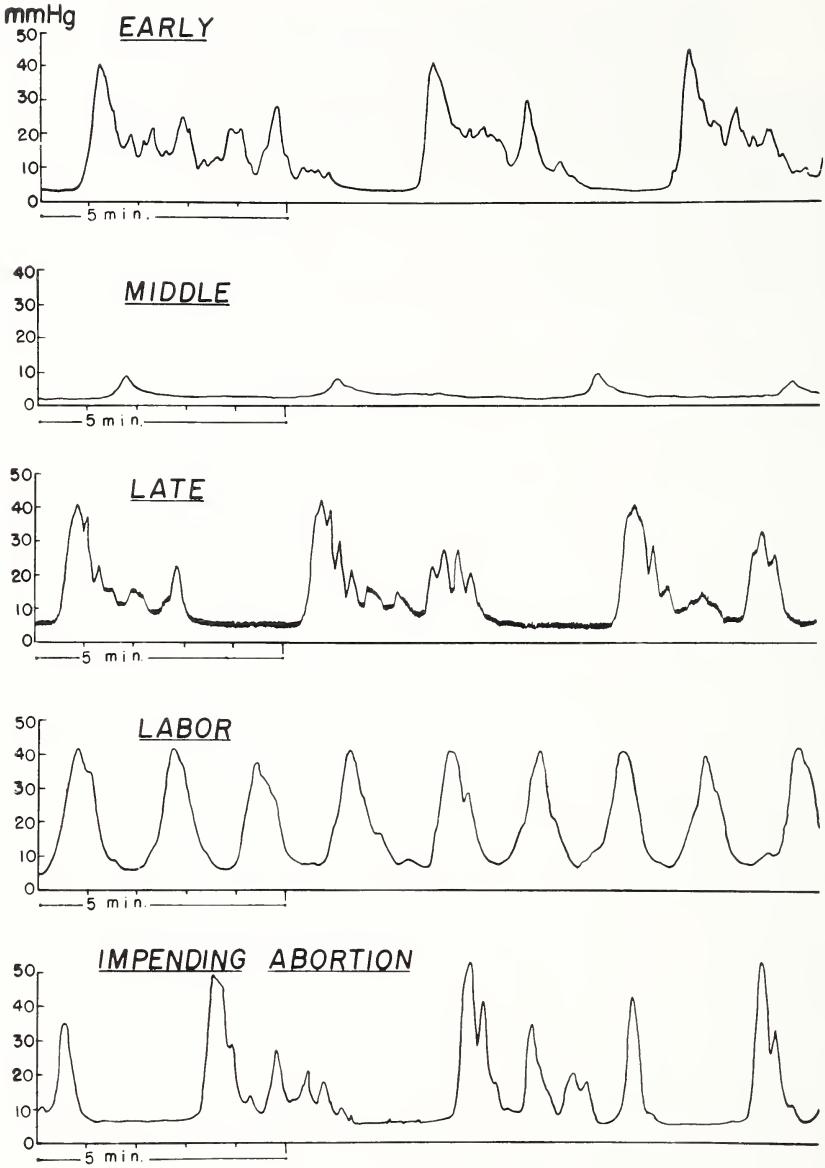

Figure 16.—Tracings of intrauterine pressure recordings in monkeys at three stages of pregnancy, in labor, and at the time of impending abortion. Early pregnancy, Monkey 16A, 66 days; midpregnancy, Monkey L–53, 119 days; late pregnancy, Monkey 6B, 153 days; labor, Monkey 940, 148 days; impending abortion, Monkey 8A, 140 days (abortion on day 142). Reprinted, by permission, from Donner, M. W., Ramsey, E. M., and Corner, G. W.: Maternal circulation in the placenta of the Rhesus monkey: A radioangiographic study. *Amer J Roentgen 90: 638–649 (Sept) 1963.* (Courtesy of Charles C. Thomas, publisher.)

films made following an arterial injection carried out by the technique previously described. The implication of these films is that the same spiral arterioles do not discharge their contents into the intervillous space in every instance. The question is *how is such diversity brought about?*

Fremont-Smith. Are you suggesting intermittency of arterial flow?

Ramsey. Yes. One might suppose that this is caused by the powerful myometrial contractions clamping down upon the vessels from outside. What we see in figure 20 suggests that there may be an intrinsic mechanism in each individual spiral arteriole. This is something we must investigate further; we do not now know what the mechanism is whereby the spiral arterioles operate independently.

Fremont-Smith. Are there any sympathetic nerves?

Ramsey. There are no sympathetic nerves in the endometrial portion of the spiral arterioles.

Fremont-Smith. In the human adult, the individual terminal arterioles in the nailbed operate independently. This, however, is under sympathetic control, and when sympathetics are cut, they no longer operate separately. That is the reason I asked about the sympathetic innervation of the uterus.

Ramsey. My answer to your previous question about this was correct but incomplete. We do not think that there is nervous innervation of the portion of the artery which traverses the endometrium, but it is clear that there is innervation up to the myometrial junction. Furthermore, in the studies of the menstruating mucosa, as well as in the studies of the pregnant monkey, it has become increasingly apparent that the constrictions which occur take place just before the vessel penetrates the endometrium.

Segal. Dr. Fremont-Smith commented on the innervation and the behavior of capillaries in the nailbed. In this connection, Ling, Lawder, and de Maria[1] at the University of British Columbia have just shown a constant relationship between cortical and hypothalamic electrical activity, and the potentials emanating from the myometrium during a uterine contraction. This work was done in pregnant cats. The EEG changes in the cortical and hypothalamic areas always preceded the myometrial activity. I wonder whether the release of pressor amines could explain some of your findings on the intermittency of spiral artery flow?

Ramsey. I don't know the answer to that, but I am grateful for the suggestion. It is something to look into.

Fremont-Smith. Do you mean that these chemicals potentiate nerve stimulus, or do you mean that a chemical flowing down the arterial tree might lead to intermittency in the terminal arterials?

Segal. The former—the nervous activity liberating the substance locally.

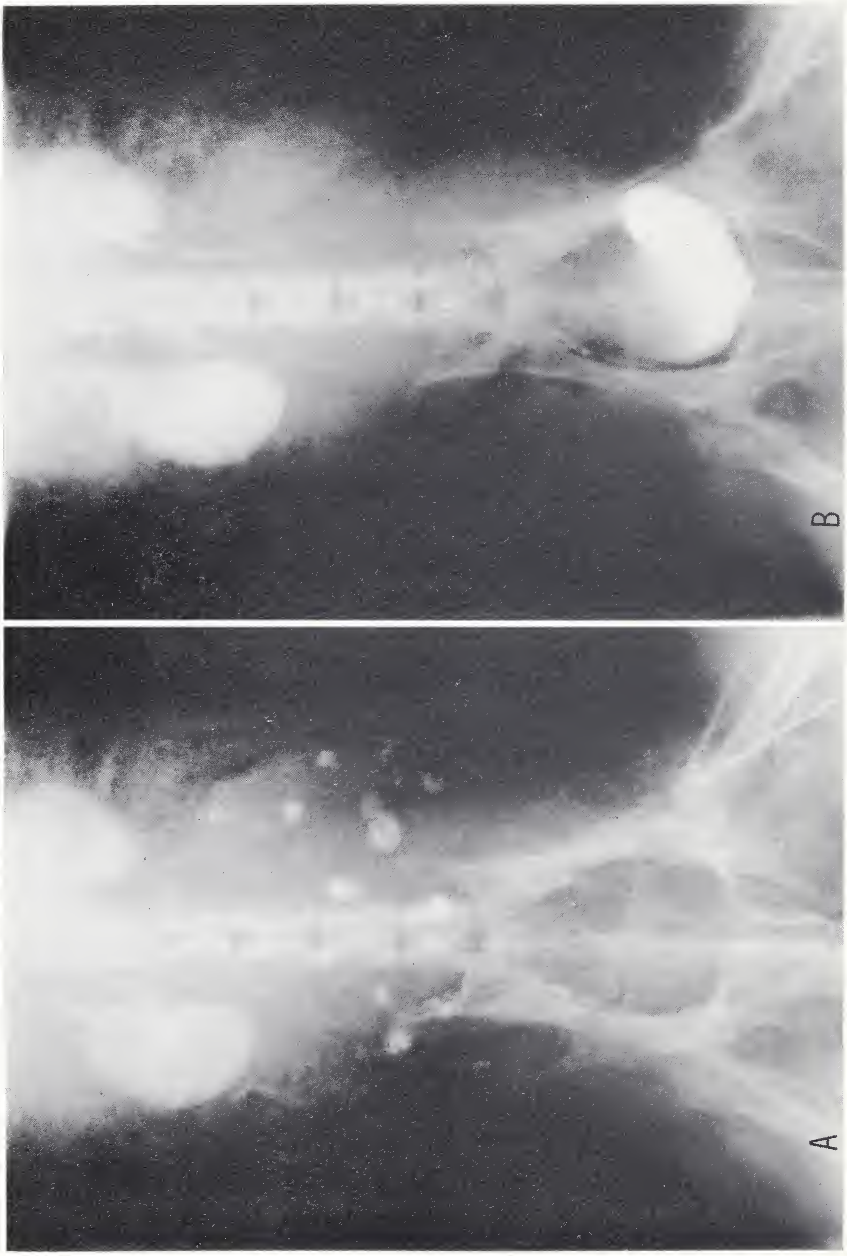

Figure 17.—Photographs of radiograms made 10 seconds after injection of radiopaque dye during (*A*) relaxation and (*B*) a strong contraction. Note absence of "spurts" in (*B*). Monkey 980 at day 87. (Reproduced by courtesy of Carnegie Institution of Washington.)

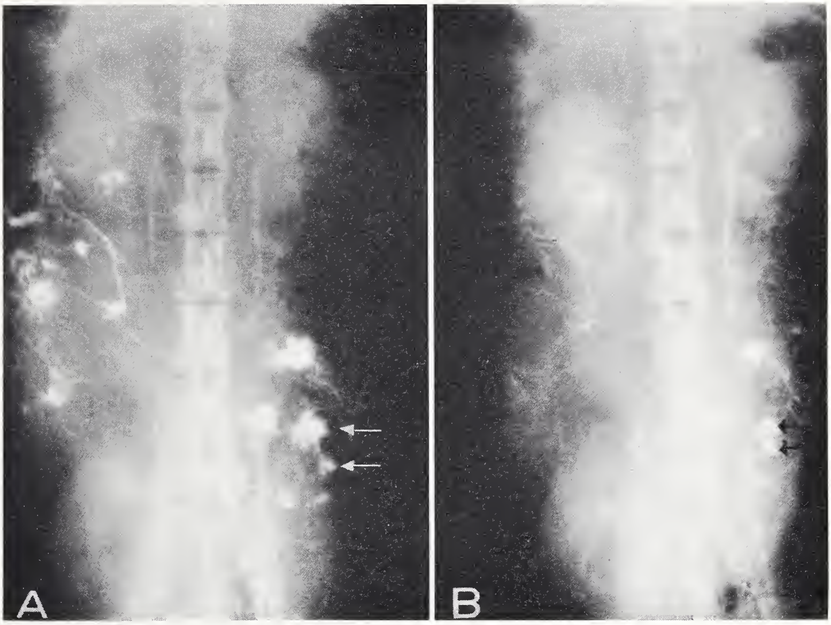

FIGURE 18.—Photographs of radiograms taken 5½ seconds after injection of a radiopaque dye during (*A*) relaxation and (*B*) a weak contraction. Arrows show two spurts which coalesce. Monkey 1B at day 117. Reprinted, by permission, from Ramsey, E. M., Corner, G. W., Jr., and Donner, M. W.: Serial and cineradioangiographic visualization of maternal circulation in the primate (hemochorial) placenta. *Amer J Obstet Gynec 86: 213–225 (May 15) 1963* (The C. V. Mosby Co., publishers).

FREMONT-SMITH. So this would require a nervous innervation at the point of terminal constriction?

SEGAL. That was the thought, yes.

FREMONT-SMITH. This apparently has been ruled out by your studies of sympathetic nerves, Dr. Ramsey.

RAMSEY. Not entirely, because the vessel might still be undergoing constriction down in the myometrium. I would like to point out one thing that emerges from this. We talk a good deal about intrauterine pressure and pressure in the spiral arterioles. We have done a good many series of studies employing four leads: one in the intervillous space, one in the amniotic cavity, one in the femoral artery, and one in the femoral vein, to determine the pressure coexisting in these four systems. This was done to test our initial postulate that circulation through the intervillous space was exclusively occasioned by the force of the maternal *vis a tergo*. In order to determine whether this postulate was correct, we needed to know what the maternal arterial blood pressure was, how much it dropped after it got into the placenta as determined from the intervillous space, and the pressure in the venous outflow.

The studies indicated that there was such a gradient and that it was adequate for maternal *vis a tergo* to be the occasioning factor in placental circulation, without the necessity for evoking some of the rather elaborate morphological structures which others had proposed. But when we were doing that work, the blood pressure leads were at some distance from the margin of the placenta—in the femoral artery and the femoral vein. For years we have been trying to get our leads closer to the placental margin so we could make our determination of effective maternal blood pressure at the point where the spurts occur. I think we have gotten our information on this point indirectly. If, for instance, inflow of arterial blood is cut off at a given level of pressure within the intervillous space, then we know that the pressure existing in the afferent arteriole must be at that level or lower, otherwise it would force its way in. It may be objected that it is a constriction of the arteriole which blocks the inflow, but that, I submit, is a matter of mechanism. What we are discussing is the actual pressure at the placental margin.

Dawes. When the uterus contracts and the amniotic pressure rises to 27 mm Hg, one supposes that no blood can flow out of the veins unless the

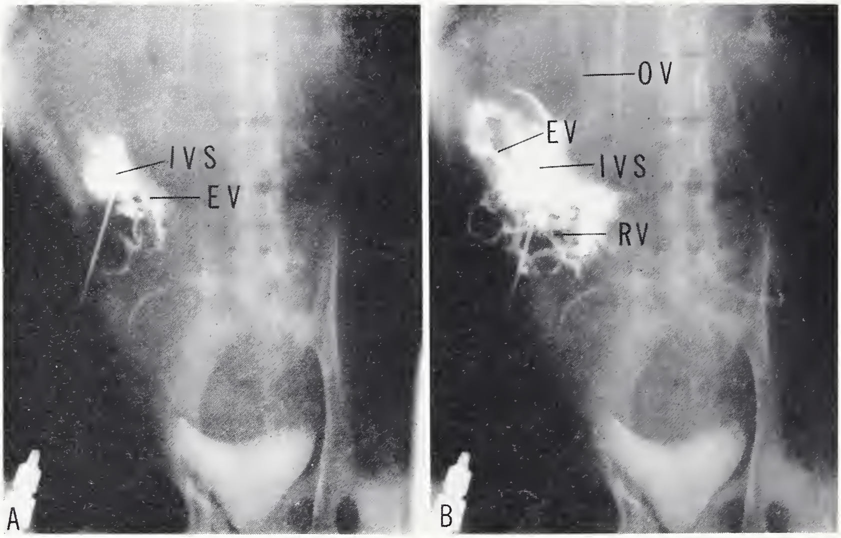

Figure 19.—Photographs of radiograms made 3 and 6½ seconds, respectively, after injection of radiopaque dye into the intervillous space. IVS=intervillous space; EV=endometrial vein; RV=radial vein; OV=ovarian vein. Monkey 62–26 at day 124. Reprinted, by permission, from Ramsey, E. M.: Circulation of the placenta. In *Birth Defects Original Article Series.* New York, The National Foundation—March of Dimes, (Apr) 1965, vol 1, pp 5–12.

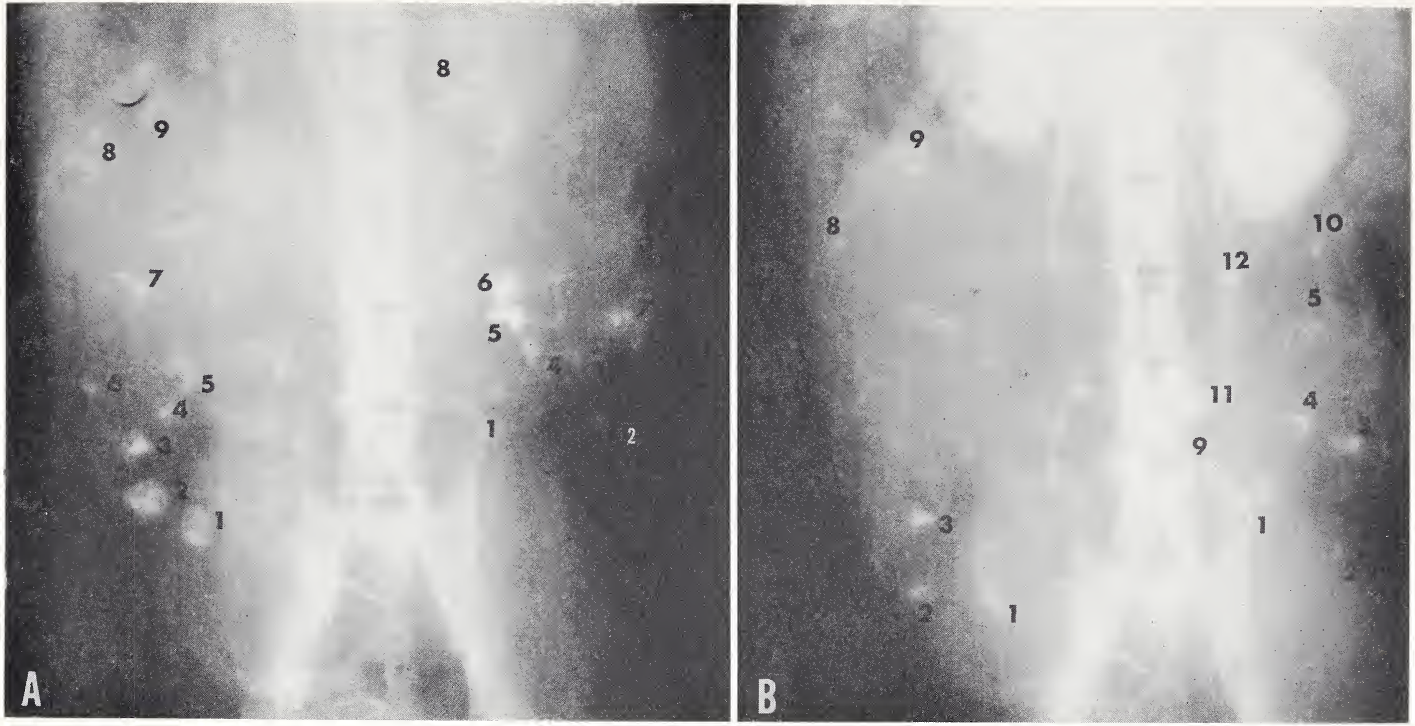

Figure 20.—Photographs of radiograms labeled to show that different arterioles are patent in two different contraction cycles. (*A*) 9½ seconds after injection during relaxation; (*B*) 11 seconds after injection during contraction. Note that entries 4 to 7 in the right placenta and 6 to 8 in the left are not seen in radiogram (*B*) but that new entries 9 to 12 appear in the left placenta. SP No. 6, Monkey 59–7, 125 days pregnant. Reprinted, by permission, from Ramsey, E. M., Corner, G. W., Jr., and Donner, M. W.: Serial and cineradioangiographic visualization of maternal circulation in the primate (hemochorial) placenta. *Amer J Obstet Gynec 86: 213–225 (May 15) 1963* (The C. V. Mosby Co., publishers).

venous pressure exceeds this value. The arteriovenous pressure across the placenta must be less. I do not think you are entitled to infer that the arterial pressure at the point of entry of the artery into the uterus is much less than that in the aorta or femoral artery. I would be amazed if this were so, because the vessels are so large. You may be studying the changes in transuterine pressure induced by the uterine contraction.

RAMSEY. You mean that circulation would fail through being blocked at the venous end?

DAWES. Yes.

RAMSEY. But we are adding a diffusible dye, as well as a dye under pressure. If it were merely sitting at the placental margin, it should diffuse in a little way into the placenta, or it should at least fill the blood vessels of the wall leading to the placental margin. We do not see this. We have lack of opacity in the arterioles during such a contraction.

DAWES. But this is over a short period of time, isn't it? The dye wouldn't diffuse up an artery, which is, after all, quite small.

RAMSEY. It goes as far as the myometrium.

DAWES. And then stops?

RAMSEY. Yes. However, these factors are pertinent. I must consider your point further.

COOK. Is there any pharmacological means of producing complete relaxation of the uterus without relaxing the arteriolar tone? If this were possible, studies could clarify the role of the endometrium in controlling the blood supply to the local areas of the uterus.

RAMSEY. This is something we would very much like to find. However, as far as I know, there is no such drug at this time.

POTTER. Do you have any idea of how much time elapses between flow of blood into the intervillous space and its return into the venous circulation?

RAMSEY. No, and this is interesting. We had thought we would be able to study the whole course of flow through the placenta with one injection into the femoral arteriole. This would have been desirable, because it would have given us several measurements in the course of a single circuit. But, in order to inject a bolus of dye which we can follow, a small quantity of dye must be used; otherwise, it becomes disseminated throughout the whole uterus and obscures the picture. The systemic blood which follows the bolus of dye dilutes it within the intervillous space to such an extent that it cannot be followed as it passes into the venous channels. Sometimes a faint trace can be seen, but not enough for adequate study. Therefore, we have had to inject directly into the intervillous space.

POTTER. Since the contrast material flows outward as soon as it gets into the intervillous space, do you assume there is a direct, rapid flow rather than a stagnation in any area?

RAMSEY. Yes, in general, but I would like to delete the word "rapid." It is a steady flow, but I am not sure yet what the time element is, quantitatively.

Caldeyro-Barcia. Dr. Ramsey, am I wrong in concluding from your work that when the uterus contracts, it shuts down the arterial inflow to the intervillous space?

Ramsey. I don't know that we can rule that out. External compression by the myometrium may play some part, though I feel that it is very difficult to see how a uniform myometrial contraction, or a contraction of the whole uterus, could be so selective in its effect upon individual arterioles.

Dawes. When myometrial tension increases, the veins must be compressed first. You will then get more contrast medium entering those areas in the intervillous space which are more distensible.

Ramsey. Yes, that's possible.

Dawes. Hence, there will be a greater concentration of contrast medium in the more distensible areas, which will become visible while the less distensible areas remain invisible.

Ramsey. I believe we must keep an open mind with respect to compression of the veins by the myometrial contraction. Recall that there was very little observable change in the pattern of venous drainage when we injected into the intervillous space during a contraction. There seemed to be a little difference in time, but not a great deal of difference in pattern.

Dawes. If the uterus is already contracted, the distensible spaces must be full. If you now inject contrast medium, there should be a large rise of pressure at the tip of your needle, which may not be perceptible as an increased resistance as you depress the plunger of your syringe.

Ramsey. You mean an arterial filling or a venous filling?

Dawes. I mean when you inject directly into the intervillous space. Consequently, without direct pressure measurement, I would not be too happy in concluding that under natural *in vivo* conditions the outflow from the veins is not impeded.

Ramsey. This can be interpreted either way. We need the crucial experiment. It is the very thing that we propose to do next; namely, give a massive dose of Syntocinon, something far in excess of anything that we have given to date, to see if the consequent myometrial contraction constricts the veins. If it does, then we will gradually reduce the dosage and see what the pressure threshold for constriction is.

Caldeyro-Barcia. To explain why some arteries remain patent and others closed, could it be, Dr. Ramsey, that the contractions do not always spread to the whole uterus? We have recorded the local activity in different areas and some contractions invade the whole uterus, but many contractions take only part of the organ while other parts remain relaxed.

Ramsey. Yes, that may well be. But before I comment further I believe Dr. Barron has some data on sheep. Didn't you find that the sheep's placental arterioles are not synchronous?

Barron. That's right. We don't have very good records of this type of thing, but it seems quite clear that the arterioles *do not* respond uniformly throughout the whole of the maternal placental circulation at any one time; they *do act* independently. In one horn, there may be a dilatation or an increased flow rate, whereas in the other there is a concomitant decrease. I suspect that this is true even within smaller segments of the placenta. This is fairly obvious when the two horns are compared when the ewe carries a singleton.

PICKERING. Have you conducted studies at precise periods following conception, to see what the change in this pattern is with advancing fetal age or placental age? The reason I ask is that we have observed a significant incidence of postmaturity in the Macaca mulatta monkey which is possibly a little greater than that in man.

RAMSEY. We find high contraction amplitude, relatively short intervals of relaxation, and a contraction wave with jagged contour in early pregnancy (fig. 16). In midpregnancy, we find a very placid type of activity, with low elevation and a long relaxation phase.

COOK. Does this activity come without any stimulation?

RAMSEY. Absolutely without any stimulation other than the placing of the catheter. In late pregnancy, we see something much more like the early pregnancy pattern, yet there is a variation which is of great importance. At the early period, the intermediate troughs in the contraction waves do not fall very close to the relaxation level. In late pregnancy they fall progressively closer to the relaxation level. In other words, the very complicated, complex wave is becoming organized. It is breaking up into waves of the type seen in labor which are apparently the only kind effective for the evacuation of the uterus. In labor there is high amplitude, a very simple wave, and the contractions occur at short intervals.

In impending abortion, which we have learned to diagnose from the recording, the pattern is similar to that of late pregnancy, with the complex waves breaking down and occurring more and more rapidly until the effective uterine contractions of labor are achieved.

FREMONT-SMITH. Are you suggesting that the initiation of labor may be partly dependent upon an organization of the waves into the final type that you speak of?

RAMSEY. Yes. I think I can also say that the group in Cleveland and, I imagine, the group in Montevideo, too, feel that this is the basic element.

CALDEYRO-BARCIA. This has been our belief since 1950.

JAMES. What effect does the density of the injected dye in relation to the density of blood have in your interpretation of flow? For example, if the dye were considerably more dense than blood, would this influence the picture when you inject into a very small space?

RAMSEY. On the basis of our observations to date, I think it would influence it only in that the dye would remain longer in the little pockets and crevices and blind alleys among the villi. I think you are leading up to the question of whether this method can be used as a flow-time measure. We haven't felt that it could, because of this residual effect.

Dr. Caldeyro-Barcia has made observations that have much in common with ours.

Caldeyro-Barcia. Before showing our material, I would like to review some studies made in human beings by Borell, Fernström, Ohlson, and Wiqvist [2] at the Karolinska Institute in Stockholm, which confirms the work done on the Rhesus monkey by Dr. Ramsey.

Using a similar method, these workers studied the uteroplacental circulation and measured the time of appearance of the contrast medium in the uterine artery, the intramural arteries, the intervillous space, and the uterine veins, with the uterus relaxed and contracted. Injection was made into the aorta. The studies were performed at midpregnancy, and the contractions were elicited either by intravenous infusion of oxytocin or by intraamniotic injection of hypertonic saline solution, in cases of legal abortion.

The first three columns of figure 21 show the time of appearance of the contrast medium in the intramural arteries. The films were taken every 1½ seconds. When the uterus was relaxed, the time of appearance of the contrast medium in the intramural arteries was 1½ seconds in eight patients and 3 seconds in four patients. Time was measured from the moment in which the contrast medium was first visualized in the hypogastric artery.

When the uterus was contracted, there was no change in four patients; in five, there was a delay, and in three, the intramural arteries were not filled at all. When the injections were made during the descending phase of the contraction, the time of appearance of the contrast medium in the intramural arteries was a little more delayed than with the relaxed uterus. With the relaxed uterus, the average time of appearance of contrast medium in the intervillous space was about 4½ seconds. When the uterus was contracting, no contrast medium was seen in the intervillous space in nine patients. In two patients, it was greatly delayed. In another two, it was similar to that obtained when the uterus was relaxed.

The wide disparity obtained when the uterus was contracting might be explained by changes in the spreading pattern of uterine contractions. When these invade the area of myometrium underlying the placenta, the vessels supplying the intervillous space are compressed and it is not filled. If the placental area is spared by the contraction, the intervillous space is filled. When the injections were made during the descending phase of the contraction, the vascular effects were less marked than during the ascending phase.

The time the contrast medium appeared in the uterine veins ranged between 6 and 12 seconds in the relaxed uterus. The results obtained when

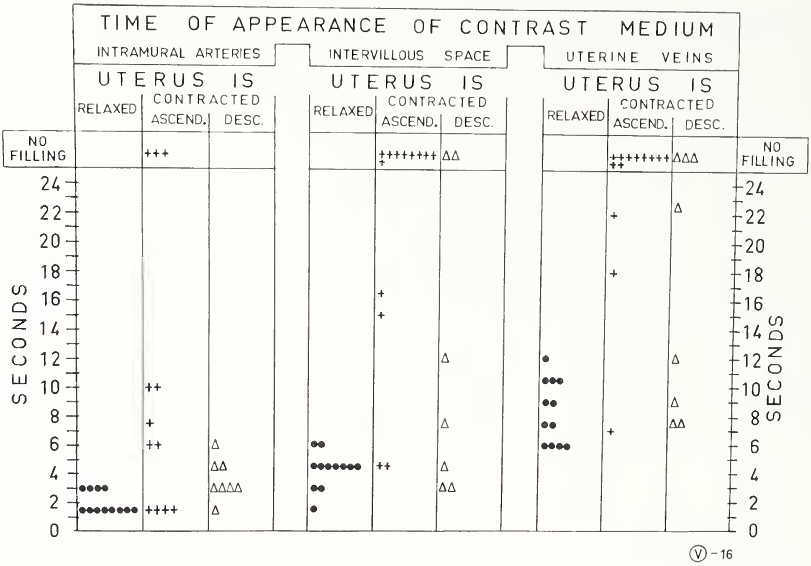

FIGURE 21.—Uterine contractions suppress or slow down the uteroplacental circulation. Data obtained by Borell et al in pregnant women with radioangiography. Time is measured from the moment in which the contrast medium appeared in the hypogastric artery. No "filling" indicates that the contrast was not visualized. When the uterus was relaxed, the contrast medium was always seen in the intervillous space, arteries, and veins. When the contrast medium was injected during the ascending phase of the contraction, the circulation was either delayed or absent (no filling). (Chart built by Aramburú, G., and Caldeyro-Barcia, R., with data from Borell, U., Fernström, I., Ohlson, L., and Wiqvist, N.: Effect of uterine contractions on the human uteroplacental blood circulation. *Amer J Obstet Gynec 89: 881–890, 1964.*)

the uterus was contracted were similar to those reported for the intervillous space.

In summary, the circulation through the intramural uterine arteries, the intervillous space, and the veins is either delayed or cancelled when the injection of the contrast medium in the aorta is made during the ascending phase or near the peak of a uterine contraction. The Swedish group found that with the relaxed uterus, the uterine artery remained filled with contrast medium for 4½ seconds, whereas with the contracting uterus, this time was much more prolonged. Similar results were found for the intramural arteries.

These results compare very well with those of Dr. Ramsey. The area of the myometrium underlying the placenta contracted in the large majority of cases; no evidence is found of a local inhibitory effect of the placenta on uterine contractions.

Klaus. When you say that an area is not filled with dye, couldn't there still be flow which you do not visualize because the dye might be more spread out?

Caldeyro-Barcia. The investigators stated that they couldn't see the vessels or the intervillous space.

Dawes. If a blood vessel is sufficiently small it may be invisible on cineangiography, even though it is full of contrast medium. Also, a wide vessel may be invisible if the contrast medium is diluted and the structures above and below it are sufficiently radiopaque. Therefore, positive observations by cineangiography may be convincing, but negative ones must be considered cautiously.

Klaus. So there may be flow here that we just don't see?

Dawes. Right.

Caldeyro-Barcia. Would there be less flow, that is, the vessel would have lesser caliber than when you do see it?

Dawes. You may be able to get an estimate of circulation time, but you cannot deduce flow. We have catheterized the femoral artery of fetal Rhesus monkeys and returned the leg within the uterus. As one would expect, the arterial O_2 saturation fell shortly after the peak of a strong uterine contraction.

Ramsey. My own experience,[3] with respect to this point, agrees with the findings of Borell et al. The time the dye is injected during the course of the contraction wave is all-important. If it is introduced too low on the ascending limb of the wave, it enters the intervillous space perfectly well because the pressure hasn't reached threshold. If it is injected too near the peak, it will reach the intervillous space as relaxation is commencing, and it will go in just as if the uterus were in tonus. To show the effect of contraction, the optimum time for injection is halfway up the ascending limb of the contraction wave.

The conservative and safe rule to follow in interpreting X-ray results is the concept of "all or none," because of the dilution factor which Dr. Dawes mentioned and because of the lag in clearance that we have encountered. These factors produce both positive and negative results which can confuse the picture. As a result, flow time is not very well calculated by our present techniques of radioangiography, although I would suspect that it might be easier to use this test in humans than in monkeys. The smallness of the monkey creates difficulty in visualization.

One other appealing thing about the Stockholm group's report is that they speak only of the "contracted" or "uncontracted" uterus and do not attempt to set a threshold value for the observed phenomena. To date, we haven't been able to do this either in our 60 or more observations. We find inflow cut down in one monkey at 7 mm Hg above tonus, yet in another blood may continue to enter the intervillous space at 30 mm Hg. We will probably be able to determine threshold some day, but right now the canny thing to do is to just say "contracted" or "not contracted," bearing in mind that there may be regional differences because of local variations in the passage of the contraction wave.

CALDEYRO-BARCIA. Dr. Ramsey, have you studied the influence of the systemic arterial pressure in the level at which circulation would be influenced or arrested by uterine contractions? In other words, did you find that if the animal was hypotensive, the vessel would be more easily closed by the contracting myometrium?

RAMSEY. We have done this only as an incidental finding. So far, we have found no influence.

CALDEYRO-BARCIA. We find a very marked influence on the effects of uterine contractions on the fetus, depending on whether the systemic arterial pressure is normal or hypotensive. The fetus is much more susceptible if the mother has hypotension.

PATTERNS OF UTERINE CONTRACTIONS

CALDEYRO-BARCIA. Since 1952 we have studied the spreading of the contraction throughout the uterus. Several microballoons are inserted into the mass of the myometrium in different areas of the uterine wall; the pressures exerted by the contracting myometrium on each of these microballoons are recorded simultaneously by pressure transducers (fig. 22).

In some instances, these microballoons have been threaded into the intramural part of uterine veins in order to record the compression exerted by the myometrium on these vessels. This was compared with the pressure exerted in the amniotic cavity, which was recorded by the catheter floating in the amniotic fluid.

AVERY. What is your reference "zero" pressure?

CALDEYRO-BARCIA. The zero we take is the intraperitoneal pressure.[4]

CLEMENTS. How large is the microballoon?

CALDEYRO-BARCIA. The volume is .02 ml. After a microballoon has been inserted into the myometrium, it is filled and slightly distended with a micro-injector.

Figure 23 shows records obtained at the 36th week of pregnancy. The intramuscular pressure was recorded simultaneously in the uterine fundus and in the inferior part of the upper segment. There are two Braxton Hicks contractions which invade both parts of the uterus and produce elevations of 25 mm Hg in the amniotic pressure. In between the Braxton Hicks contractions, there are small contractions which remain localized to one area of the uterus. Contraction 1 is confined to the inferior part of the upper segment where it causes a rise of 20 mm Hg in the intramyometrial pressure. It causes a rise of approximately 3 mm Hg in the amniotic pressure and has no visible effect on the tracing of intramyometrial pressure

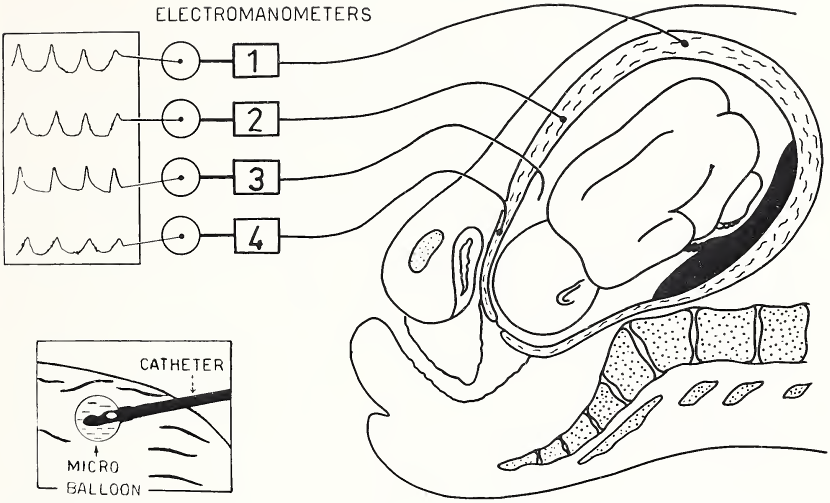

Figure 22.—Method of recording uterine contractility. The amniotic pressure is recorded by means of the catheter introduced into the amniotic cavity and connected to the electromanometer No. 3. The intramyometrial pressures in the fundus, midpart, and lower segment are recorded simultaneously by means of three microballoons introduced into the mass of the myometrium, each of which is connected by a catheter to an electromanometer. In the lower left-hand corner, a microballoon inserted into the mass of the myometrium is shown in detail. Reprinted, by permission, from Caldeyro-Barcia, R., and Alvarez, H.: Abnormal uterine action in labour. *J Obstet Gynaec Brit Comm 59: 646–656 (Oct) 1952.*

recorded from the uterine fundus. Contraction 2 is confined to the uterine fundus where it raises the intramyometrial pressure by 22 mm Hg. It causes a rise of approximately 5 mm Hg in the amniotic pressure and has no effect on the record of intramyometrial pressure obtained from the inferior part of the upper segment. I feel this record shows very clearly that the intramyometrial pressure is not influenced by the contractions of distant areas and that it constitutes a good method for studying the contractility of the muscle surrounding the balloon. These small local contractions are typical of uterine activity in women during pregnancy.

Figure 24 shows a record obtained during normal first-stage labor, in which all the contractions begin in the right side of the uterus and from there spread to the left side. The first contraction starts in the right side at the moment indicated by the vertical line A and takes approximately 15 seconds to reach the microballoon inserted into the left side of the uterus. The area surrounding that microballoon starts contracting at the time marked by the vertical line B. At that moment, the intramyometrial pressure of the right side has already increased 50 mm Hg above the baseline. This strong contraction of the right side produced a passive elevation of

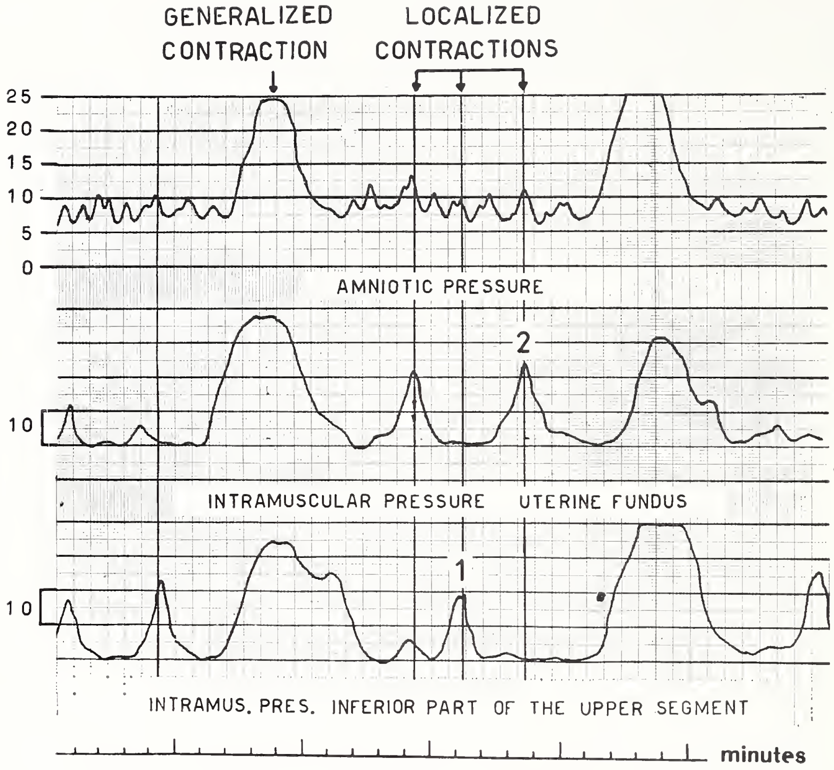

Figure 23.—Record obtained in the 36th week of pregnancy. It shows two Braxton Hicks (generalized) contractions and several small (localized) contractions. Reprinted, by permission, from Alvarez, H., and Caldeyro-Barcia, R.: Studies on the contractility of the pregnant uterus. In *Proceedings of the First World Congress on Fertility and Sterility.* New York, International Fertility Association, 1953, vol 2, pp 217–241.

intramyometrial pressure in the left side of only about 5 mm Hg. The differences in slope between the passive stretch and the active contraction can easily be appreciated on the tracing of intramyometrial pressure obtained in the left side of the uterus.

The peak of the contraction in the right side precedes that in the left side by a few seconds. In spite of this small difference, there is good coordination between the right side and the left side of the uterus. This coordination is reflected on the record of the amniotic pressure when the contractions have a regular shape with one peak only. One can also see that the compression exerted by the contracting myometrium on a microballoon inserted in the thickness of the uterine wall is two or three times higher than the pressure exerted on the amniotic cavity. This might explain why normal contractions, causing a rise of 50 mm Hg in intraamniotic

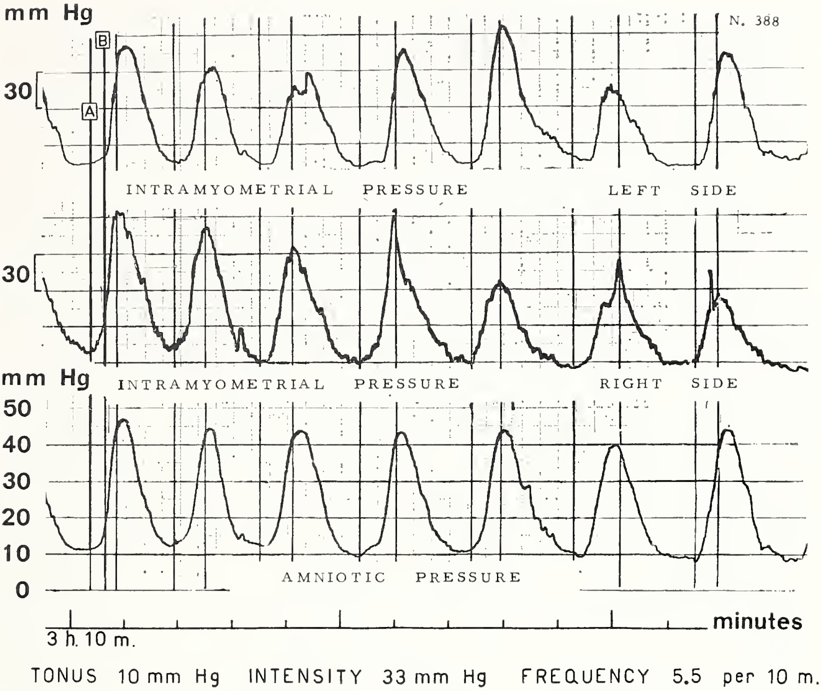

Figure 24.—Record obtained in the first stage of normal labor. The amniotic pressure and the intramyometrial pressure at the left and right sides of the fundus are recorded simultaneously. At the bottom are shown average values corresponding to the amniotic pressure tracing. The contractile wave spreads in a regular form reaching first the right and then the left side. Reprinted, by permission, from Alvarez, H., and Caldeyro-Barcia, R.: Studies on the contractility of the pregnant uterus. In *Proceedings of the First World Congress on Fertility and Sterility.* New York, International Fertility Association, 1953, vol 2, pp 217–241.

pressure, are able to interfere with blood flow through the intramural portion of uterine arteries as Dr. Ramsey and also the Swedish group found.

It is worthwhile to compare this with the record of amniotic pressure shown in figure 25, in which the contractions were of an irregular shape, usually with two peaks, caused by the incoordinate contractions of the two sides of the uterus. Number 1 indicates the peak of one contraction on the left side of the uterus, which occurs when the right side is completely relaxed. The contraction apparently remained localized to a small area of the left side and produced a small rise in the amniotic fluid pressure (*No. 2*). In this example, it is also clear that the contraction of the left side of the uterus, which produced a moderate rise in the intraamniotic pressure, did not produce any passive rise in the intramyometrial pressure in the right side. The active contraction of the right side started when contraction

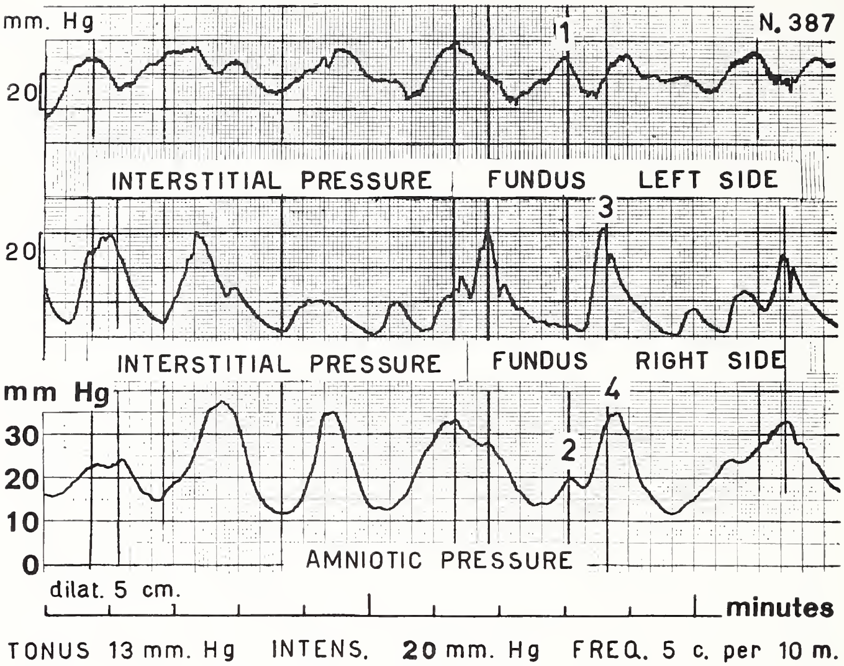

FIGURE 25.—Incoordination between the right and the left side of the uterus. Same method of recording as in figure 24. Reprinted, by permission, from Alvarez, H., and Caldeyro-Barcia, R.: Studies on the contractility of the pregnant uterus. In *Proceedings of the First World Congress on Fertility and Sterility.* New York, International Fertility Association, 1953, vol 2, pp 217–241.

No. 1 of the left side had almost finished. The right side contracted strongly (*No. 3*) and caused a marked increase in the amniotic pressure (*No. 4*).

I think these examples clearly demonstrate that the intramyometrial balloons are primarily influenced by the active contraction of the surrounding myometrium. They are influenced very little, if at all, by the contractions in more distant areas. Not all of the events recorded in the amniotic pressure tracing can be explained if we record the intramyometrial pressure in only two areas of the uterus. There are many other areas of the uterus influencing intraamniotic pressure from which we have obtained no information at all.

The contractions which do not invade all of the uterus might spare the placental area and explain why, in some instances, the intervillous space is filled by contrast medium, even when the injection is made during a uterine contraction. Perhaps, if it were possible to combine radioangiographic studies with records of intramyometrial pressure, we could understand better the effect of uterine contractions on uteroplacental circulation.

AVERY. Were these air-filled balloons?

CALDEYRO-BARCIA. No, the whole system is filled with water. It is completely bubble-free.

RAMSEY. Dr. Caldeyro, did you ever develop a balloon small enough to use in the monkey myometrium? I remember, some years ago, we discussed this and you said, "I guess we just can't use balloons."

CALDEYRO-BARCIA. I now think the technique can be used.

RAMSEY. Even though the myometrium at term is less than a millimeter?

CALDEYRO-BARCIA. Yes, by using a fluid-filled needle without a balloon at the end. Hendricks [5] has recorded the intramyometrial pressure by inserting a catheter into the uterine wall without a balloon at the tip. The advantage of the microballoon is that it acts as an anchor, whereas the tip-free needle might move and change its position in the myometrium.

SEGAL. Do the mechanical devices that exert a negative, extraabdominal pressure influence the blood flow?

CALDEYRO-BARCIA. I don't know.

RAMSEY. Would you anticipate, Dr. Caldeyro, that a very large dose of oxytocin would bring about a coordinated or an uncoordinated uterine contraction?

CALDEYRO-BARCIA. In women, when you raise the level of oxytocin in the blood above certain limits, you get a contracture which is completely unphysiologic.

RAMSEY. Is the contracture uniform?

CALDEYRO-BARCIA. Yes. It is generalized, uniform, and sustained. I think you will find the same results in the Rhesus monkey.

RAMSEY. I think we will have to do something unphysiologic like that in our series.

CALDEYRO-BARCIA. To produce more unphysiologic effects, you had better use the ergot alkaloids which will give a stronger and more generalized contraction.

COMROE. Have you ever measured pressures at different parts of the uterine wall—outside, middle, or near the interior?

CALDEYRO-BARCIA. We haven't, but this has been done in the puerperal uterus by Eskes [6] who found that the intramyometrial pressure is different at different depths. There are areas of the uterine wall in which the contractions cause a greater pressure rise than in other areas. I think this is due to the fact that the fibers are arranged like a network, forming spirals around the vessels. This might explain the strong influence of uterine contractions on myometrial circulation.

COMROE. How do the blood vessels to the placenta go through the myometrium?

RAMSEY. Let's take the nonpregnant first. The great external arteries enter the myometrium at a sharp angle and at once turn to form an arcuate network in the middle third of the wall. From this, radial arteries come off almost at right angles, penetrating the junction between myometrium

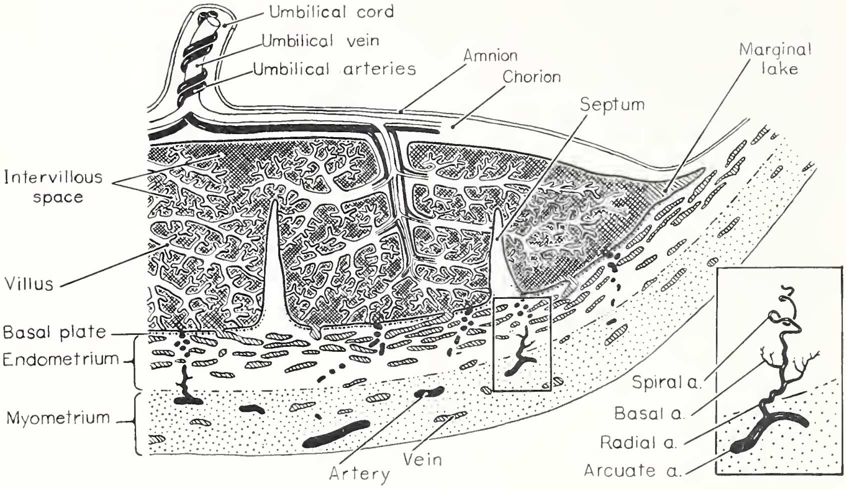

Figure 26.—Diagrammatic representation of a portion of the primate (hemochorial) placenta attached to the uterine wall. The inset shows, at higher magnification, the components of a single arterial stem. Reprinted, by permission, from Ramsey, E. M.: Uterine and placental circulation. In *Respiratory Problems in the Premature Infant: Report of the Fifteenth M & R Pediatric Research Conference.* F. W. Heggeness, editor. Columbus, M & R Laboratories, 1954, pp 23–34.

and endometrium. These divide into the more prominent spiral arterioles and the little basal ones which only nourish the uterine wall itself and are unimportant for our present consideration. The spiral arteries rise vertically to the endometrial surface and eventually communicate with the placenta (fig. 26). As pregnancy progresses, these spirals are diverted to an oblique course. Where they penetrate the myometrial-endometrial junction, the media changes its character and loses its nervous innervation. The more distal portion, that within the endometrium, is that which is destroyed by the menstrual slough and is reconstituted in successive cycles.

Comroe. I particularly wanted to know whether the vessels were distributed uniformly throughout the whole myometrium.

Ramsey. It is uniform throughout the myometrium, but as pregnancy progresses there is obliteration of the inner vascular network. It is compressed and reconstituted after delivery.

Fremont-Smith. How is it different directly opposite the placenta?

Comroe. That's what I really wanted to know.

Ramsey. What I have described is the situation at the placental base. In peripheral portions, the vascular pattern of the endometrium remains essentially the same as before pregnancy, but the vessels are mechanically compressed by the overlying conceptus. The condition in the myometrium is structurally the same as in the nonpregnant, but influenced, again, by mechanical constriction, so that, in general, the vessels become more distended and the veins in particular dilate and are visualized as clefts between the layers of the muscle.

FREMONT-SMITH. The arteries approaching the placenta are no bigger than the arteries in other parts of the uterus?

RAMSEY. They are very much bigger. Only the ones in the peripheral portion are collapsed by the pressure and become hardly visible except microscopically.

DAWES. I suppose that in a uterus which is contracting rhythmically . . .

RAMSEY. Do you mean in labor or throughout pregnancy?

DAWES. Either . . . blood flow through the myometrium must increase considerably. Has this been studied?

CALDEYRO-BARCIA. Yes, by Wright, Morris, Osborn, and Hart[7] in 1958.

DAWES. Various assumptions have been made regarding the relative amount of oxygen consumed by the placenta and myometrium. We need to know the blood flow and oxygen consumption of these organs.

SEGAL. Do the studies of Misrahy, Beran, and Hardwick[8] on oxygen tension of the brain of the fetus, in response to oxytocin and manipulation, relate in a compatible or in a grossly incompatible way to the flow data?

CALDEYRO-BARCIA. They fit very well, since Misrahy et al[8-10] find that uterine contractions cause a transient drop of the oxygen availability in the fetus.

POTTER. We have long been struck with the difference in the muscular pattern of the outer one-third and the inner two-thirds of the human myometrium. The major blood vessels, as they enter the uterus, run longitudinally to some extent, although circularly, too, in an area between the outer one-third and inner two-thirds of the uterine cavity. The muscle exterior to this is very irregular in pattern. It is intermixed with a good deal of connective tissue. It has seemed to me that anyone, in studying reaction of muscle strips, must be sure of where the muscle is taken, because the pattern in the outer third looks as if it should have a much poorer contractility than the inner two-thirds.

The endometrium in a pregnant uterus at term prior to delivery is thinned down to less than a millimeter and the myometrium is many times thicker than the endometrium. In the region of the placental site there is a marked proliferation of blood vessels as well as an increase in size of both arteries and venous channels. A few years ago we had an opportunity to inject a number of intact uteri at different stages of gestation. There are many more vascular channels in the region of the placental site than in other parts of the uterus. In the uterus immediately after delivery the placental site can seldom be identified except by the presence of these vessels. If the uterus is opened, laid flat, and cut into 1 cm sagittal sections with a brain knife, the placental site can be identified by the more numerous and more dilated vascular channels.

As the uterus recovers following pregnancy, the placental site vessels actually become isolated and pushed up above the surface and gradually expelled. I couldn't believe this until we actually did hysterectomies 1 day, 2 days, 3 days, and so on, following delivery. Each time a new pregnancy begins, the uterus is almost like a nulliparous uterus, regardless of the number of previous pregnancies. There is not only a change in the vessels themselves during pregnancy, but also in the number of vessels and in the total pattern of the placental site area.

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Fetal Circulation

Dawes. For many reasons, we would like to get a measure of placental function, but this is not easy. I have therefore decided to restrict my interest in the first instance to umbilical blood flow through the *fetal side* of the placenta. All the experiments were done on fetal lambs delivered by cesarean section under light chloralose anesthesia.[1] The earliest gestation age used was 80 to 90 days, when the lamb weighs 300 to 650 gm, while at term (about 147 days) it weighs 3 to 6 kg. The lamb may be delivered still attached to the mother by its umbilical cord, and remain in good physiological condition for long periods of time.

Ramsey. In the sac?

Dawes. No, outside.

Comroe. What does chloralose anesthesia do?

Dawes. I don't know.

Comroe. Why don't you use spinal anesthesia?

Dawes. We have done so but prefer light chloralose anesthesia. Dr. Barron has used this for many years and will, I hope, agree.

Figure 27 shows the relation between umbilical blood flow and gestational age. The open circles in figure 27 show measurements of umbilical blood flow made by earlier, rather clumsy methods. The closed circles are measurements made more recently, using a cannulated type of electromagnetic flowmeter. With either method, umbilical flow increases greatly with gestation age, and with the more recent method flow is greater.

Figure 28 shows the relationship between umbilical blood flow and O_2 consumption in lambs of 80 to 90 days gestation age. The O_2 consumption was calculated as the product of umbilical flow and the arteriovenous O_2 difference. Umbilical flow was deliberately reduced by hemorrhage (○), by constriction of the abdominal part of the umbilical vein (●), or by constriction of the descending aorta (⊖). At this gestational age umbilical blood flow is very high, averaging nearly 250 ml/kg/min. Only when flow is reduced to 120 ml/kg/min or less does fetal O_2 consumption begin to fall. At this age fetal O_2 consumption is 5.4 ml/kg/min, while at term it is sig-

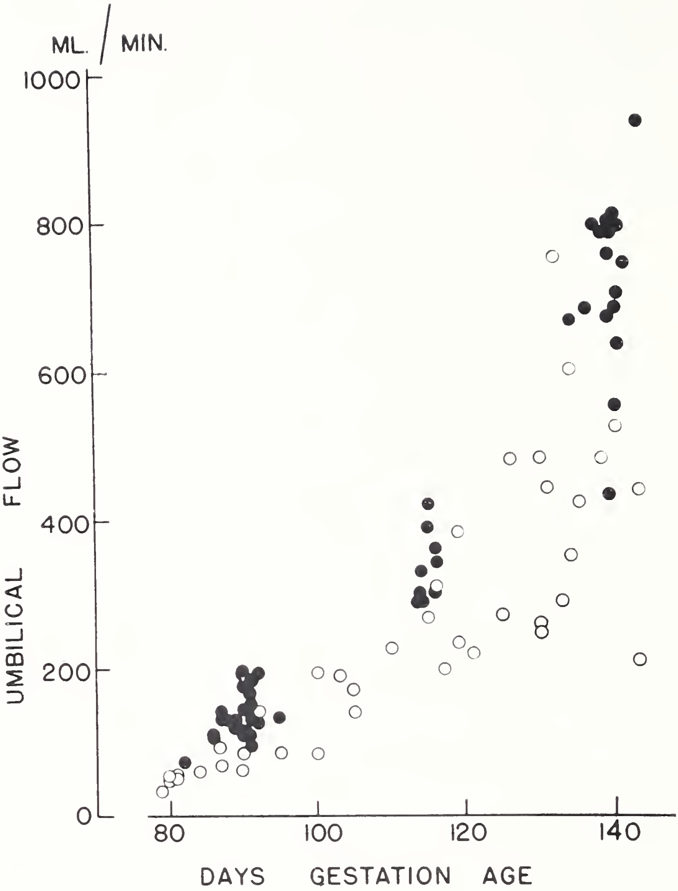

FIGURE 27.—Umbilical flow in fetal lambs plotted against gestation age to compare the results using an electromagnetic flowmeter under chloralose anesthesia (●) with those obtained by venous occlusion plethysmography (○). Reprinted, by permission, from Dawes, G. S.: The umbilical circulation. *Amer J Obstet Gynec 84: 1634–1648, 1962* (The C. V. Mosby Co., publishers).

nificantly less, 4.6 ml/kg/min. It could be that in the mature fetus there is more skin and bone. These measurements are difficult to interpret because we do not know what determines the resting O_2 consumption of the fetus *in utero*. This is one thing we should like to know. In all events there is an adequate reserve of umbilical blood flow.

In the lamb the rate of O_2 consumption of the fetus is close to that of the mother, and it is uncertain whether this is a causal association or coincidental.

The lamb was delivered and the abdomen was opened to explore the abdominal portion of the common umbilical vein. The lamb was given

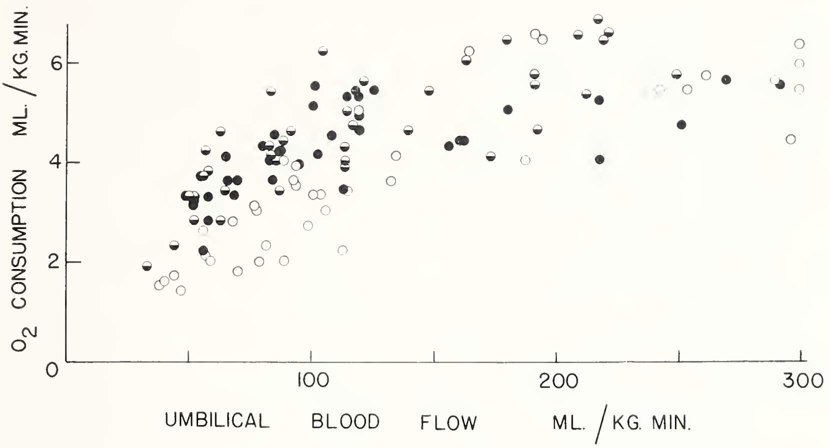

FIGURE 28.—Immature fetal lambs (80–90 days gestation). O_2 consumption falls as umbilical blood flow is reduced by constriction of the aorta or umbilical vein, or by hemorrhage. Reprinted, by permission, from Dawes, G. S., and Mott, J. C.: Changes in O_2 distribution and consumption in foetal lambs with variations in umbilical blood flow. *J Physiol (London) 170: 524–540 (Apr) 1964.*

heparin intravenously. The vein was divided and the cut ends rejoined by a loop containing a cannulated electromagnetic flowmeter.[2] This is an accurate instrument and the pressure drop across the loop is trivial compared with that between the aorta and the inferior vena cava. The vein is divided and joined up again usually in less than 2 minutes, and the fetus recovers within 5 to 10 minutes.

In lambs near term the mean aortic pressure is about 64 mm Hg. The pressure drop from the aorta to the cotyledonary arteries is about 10 mm Hg. There is a much larger drop between the cotyledonary arteries and veins (40 mm Hg). The pressure drops across the umbilical veins (4 mm Hg) and the liver (10 mm Hg) are relatively small. Hence, most of the vascular resistance in the umbilical circulation is in the fetal villi. Since more than half the cardiac output passes through the placenta, small changes in resistance in the fetal villi might have a large influence upon the distribution of blood flow in the fetal circulation.

Measurements of umbilical flow were made while arterial pressure was lowered by constriction of the aorta, or venus pressure was raised by constriction of the umbilical vein. From these measurements, mean pressure-flow diagrams were constructed in lambs of three gestational ages, 90, 115, or 140 days. Figure 29 shows that between 90 and 115 days the mean vascular pressure drop across the fetal side of the placenta, between aorta and umbilical vein, rises from only 30 to 35 mm Hg, but umbilical blood flow more than doubles, approximately in proportion to the increase in fetal

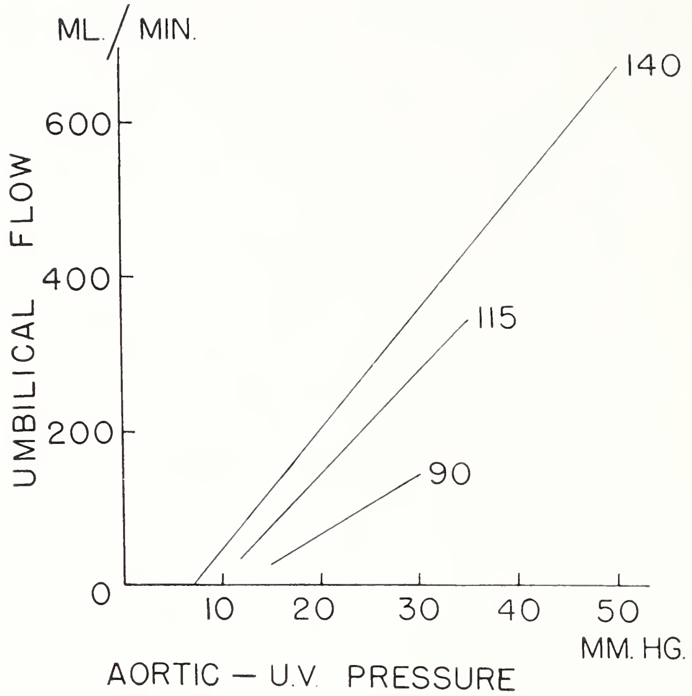

FIGURE 29.—Pressure-flow diagrams for the umbilical circulation in lambs of 90, 115, and 140 days gestation age. Reprinted, by permission, from Dawes, G. S.: The umbilical circulation. *Amer J Obstet Gynec 84: 1634–1648, 1962* (The C. V. Mosby Co., publishers).

weight. There has evidently been a large decrease in umbilical vascular resistance. Between 115 and 140 days the situation is quite different. The umbilical vascular resistance, as indicated by the slope of the pressure-flow regression lines, is not significantly altered, and the increase in flow is almost wholly attributable to a rise in arterial pressure.

From this limited point of view, one may conclude that the placenta in the sheep continues to grow only up to 115 days gestation. It may continue to elaborate after that, as shown by histological studies, but the only way the fetus can get more blood through it is by increasing the arterial pressure and this it does. A natural corollary of this deduction is that at term a heavier fetus should have a higher blood pressure, and this is so. In a series of lambs of 137 to 142 days gestational age, weighing 2.4 to 6 kg, there was a highly significant regression of arterial pressure on weight.

So far as this evidence goes, it would appear that the fetus has to make do with the placenta with which it is endowed. We do not know whether the growth of the fetus modifies that of the placenta, though there is much evidence that pathological changes in the placenta may affect the growth of the fetus. If the placenta is infarcted, it would seem as if all the fetus can do is to increase its arterial pressure, and hence increase the velocity as well as the volume of blood flow through the placenta.

In a large lamb with an average-sized placenta, the velocity of blood flow through the umbilical circulation and, what may be of crucial importance, through the area of gaseous exchange, may be higher than in smaller lambs.

It is well known that toward term—using sheep in the experimental conditions which I have described—there is a tendency for the arterial O_2 saturation to fall. Some fetal lambs at term may have an arterial O_2 saturation of more than 60 percent, but occasionally we have encountered large lambs, of 4 to 6 kg weight, with a normal O_2 consumption but an arterial O_2 saturation of less than 40 percent. They appear to be able to survive by maintaining a large umbilical blood flow.

To give a specific example, one of a series of such lambs had an umbilical arterial O_2 saturation of 35 percent and an umbilical venous saturation of 55 percent with an O_2 consumption within the normal range. Umbilical blood flow was reduced by hemorrhage from more than 200 ml/kg/min down to about 120 ml/kg/min. Oxygen consumption fell but both umbilical, arterial, and venous O_2 saturation rose by about 20 percent.

This phenomenon has been seen repeatedly in large mature lambs with a low initial arterial O_2 saturation, subjected to hemorrhage.[3] When the blood was returned to the lamb, O_2 consumption rose, and arterial and umbilical venous O_2 saturation fell.

I would suggest that this otherwise surprising observation can be explained in part by the reduction in the velocity of flow through the area of gas exchange in the placenta, and also by the reduction in fetal O_2 consumption.

At first these experiments appear in discord with earlier results in which umbilical flow was reduced by constriction of the umbilical vein.[4] In these circumstances arterial and umbilical venous O_2 saturation does not rise. However, when the umbilical vein is obstructed, umbilical venous pressure rises considerably and the fetal side of the placenta becomes engorged.

COMROE. What is the vascular system in the placenta? Is it open or closed?

DAWES. There are maternal and fetal villi which are sandwiched in between each other.

COMROE. Are there arterioles, capillaries, venules, or are there open sinusoids?

DAWES. There are sinusoids.

COMROE. Does edema form or not?

DAWES. I don't know.

COMROE. Have you ever examined this after you have done venous occlusions?

DAWES. Yes, but I don't think we've got a straight answer.

CALDEYRO-BARCIA. Do you have an explanation for the reduction in the oxygen consumption when the umbilical blood flow is reduced, in the bleeding experiment?

DAWES. Yes. It is curious that the oxygen consumption falls relatively more in the animals in which it is reduced by hemorrhage than in the animals in which it is reduced by compression of aorta or umbilical vein. I assume this is because, in part, the work of the heart is reduced and also, presumably, there is relative vasoconstriction in the fetal tissues during hemorrhage.

VILLEE. Does the hematocrit decrease during bleeding?

DAWES. Yes. The hematocrit falls quickly and if the hemorrhage is not too large, the blood pressure rises over a period of 5 to 10 minutes to regain the initial level. We also know that some organs in the fetus can vasoconstrict. When the blood is returned to the fetus, there is a rapid rise in hematocrit. The placenta may serve to produce rapid fluid exchange into or from the fetal circulation.

CALDEYRO-BARCIA. Because of this change in the hematocrit, there would be a loss of parallelism between oxygen content and saturation. During hemodilution, in spite of the rise in saturation, there could be a drop in oxygen content.

DAWES. Yes, I should have said that the samples were each individually analyzed for oxygen content and capacity.

COMROE. Have you perfused the umbilical vessels as an artificial system to determine the diffusing capacity of the circulation in the placenta?

DAWES. I don't think we are anywhere near that stage yet. I wish we were. I think we have a long way to go in order to learn about the problem of gas transfer across the placenta. It is quite evident that in adult physiology, the problem of gaseous exchange across the lung is much more advanced. As far as the placenta is concerned, I think we are still in the 19th century.

COMROE. Why?

DAWES. Because of a number of things. For instance, at present, one can't get blood samples from the placental veins. One has to make do with uterine venous samples which contain blood that comes both from the placenta and the myometrium. We also do not know to what extent there are shunts or changes in the maternal-fetal perfusion ratio. We also do not know the influence of the O_2 consumption of the placenta itself. This may be very important if the O_2 consumption and CO_2 production of the placenta is in series with the area of gaseous exchange. If this were so, then the O_2 consumption of the placenta might account for a large fraction of the apparent O_2 gradient between the maternal and fetal blood. As you know, the more sophisticated the measurements on the lung have become, the smaller the true diffusion gradient across the alveolar membrane has become. The same might be true of the placenta.

Comroe. But until you can control all these factors, don't you think it would be worth doing perfusion of umbilical arteries alone? You have really just been reporting on that by reducing blood flow through the fetus.

Dawes. I think it would be worth while removing the fetus and perfusing the fetal side of the placenta, and this we propose to do. I should also like to know whether measurements on other species would show the same kind of relation between fetal development and umbilical vascular resistance as in the sheep, but this is technically difficult.

Clements. You have drawn your two circulations as concurrent. Is there a possibility that they are countercurrent, instead?

Dawes. I do not think they are concurrent. The only direct evidence on this point is that of Dr. Barron who observed in rabbits that the pO_2 in the uterine vein was sometimes less than that in the umbilical artery. If uterine venous pO_2 were equal to maternal placental venous pO_2, then a concurrent circulation would be impossible.

The principal evidence for a countercurrent circulation rests on the anatomical studies of Mossmann [5] in the rabbit, and of Dr. Barron and Sir Joseph Barcroft [6] in the sheep. They were concerned with the large arteries and veins, and one must have some reservations as to whether their conclusions hold for sheets of capillaries, maternal and fetal, adjacent to one another. There is still uncertainty about the direction of flow at the area of gaseous exchange. It is more likely to be a mixture.

Comroe. Is this known for any species? Every textbook, and *The Scientific American* as well, says it is countercurrent.

Dawes. Dr. Ramsey, would you agree that it is almost certainly not countercurrent in the Rhesus monkey?

Ramsey. Nor in the human.

Comroe. What is the evidence? How is this determined?

Ramsey. By observation of anatomical injections and radiological injections and the manner in which the blood progresses. At the present time, this is perhaps more convincingly illustrated in *in vivo* injections with subsequent sectioning than in the radiological pictures I showed you. I like to use a different word than "flow" and to talk only of the pressure exerted by incoming blood. This forces the venous blood already present in the intervillous space through the nearest adjacent exit. Thus, there is no necessity for envisaging two streams passing one another. Figure 30 may make this concept clearer. As shown in panel 4 by arrows, I think that the incoming blood forces out the blood which is already there, rather than that a discrete venous stream flows toward the exit orifices in the placental base. Expressed in another way, the arterial blood, by its entrance, increases the pressure within the placental pool to such an extent that something has to give, and what gives is the venous blood immediately adjacent to an exit. This, I think, is a perfectly conceivable system. Certainly the

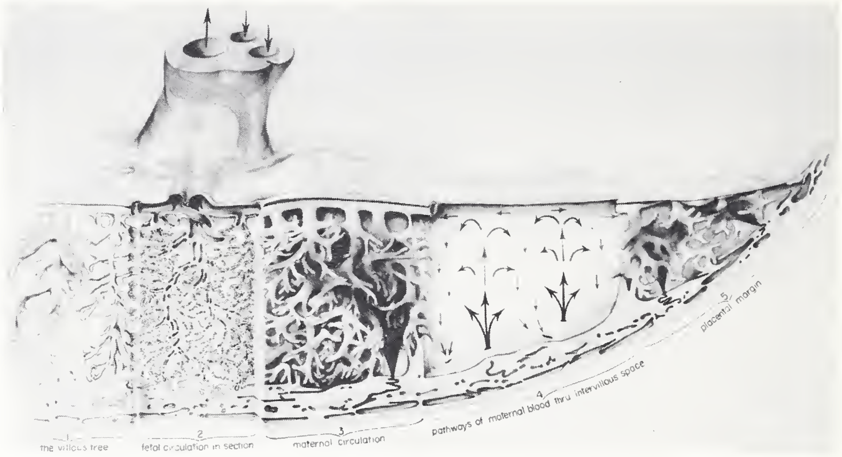
1
the villous tree
2
fetal circulation in section
3
maternal circulation
4
pathways of maternal blood thru intervillous space
5
placental margin

Figure 30.—A composite drawing of the placenta to show its structure and circulation. (Reproduced by courtesy of Carnegie Institution of Washington.)

evidence indicates this is much more likely to be the case in the monkey and the human being than is the theory of two passing streams.

Fremont-Smith. Were you talking about maternal blood or fetal blood?

Ramsey. Maternal.

Fremont-Smith. But then the question of passing streams has to do with maternal via fetal.

Ramsey. That's all right, because what Dr. Dawes said indicates that the fetal bloodstream progresses independently, and it is the passing of the maternal and the fetal streams that we are discussing. My point is that there is no set pattern of flow on the maternal side; that it is a piling up and slow dispersion in all directions. That checks with what you had in mind, doesn't it, Dr. Dawes?

Dawes. Yes. Bartels, Moll, and Metcalfe [7] have a good word for this. They describe flow as "multivillous," implying that the maternal blood flows past a series of fetal villi.

Clements. Has this ever been studied by the transfer of inert gas?

Dawes. I don't think so.

Ramsey. Not to my knowledge.

Dawes. May I return to the sheep? There is an anatomical question which has not yet been settled. According to Barcroft and Barron [6] there is a central artery in the fetal villus but no central vein. Subsequently, Wimsatt [8] has described veins in the fetal villi. If there are veins in the villi, there are probably capillary loops on the surface of the villi, and one would hesitate to say whether flow is concurrent or countercurrent; it may be a mixture of both.

Fremont-Smith. But are you not also saying, if it is divided into these multiple little loops, it will make less and less difference whether it is concurrent or countercurrent, because there won't be long areas of passing each other in opposite directions, but the areas of passage will be broken up into many small ones?

Dawes. The reason we are all so interested in this point is because we must know the relative direction of flow if we are to calculate the mean concentration gradient for gaseous exchange across the placenta.

Ramsey. Would it be a corollary that if it were one way in the primate, for instance, and another way in the sheep, it would be rather difficult to transfer conclusions?

Dawes. One learns different things from studying different species. Nature generally copes with problems in much the same way. One is happier studying mechanisms because most biological mechanisms are qualitatively similar, though quantitatively different, in different species.

Ramsey. You don't think it will be necessary, then, to go one step further somewhere along the line and find similarities between these two apparently quite different mechanisms?

Dawes. It might be.

Segal. Is there information from work with any species about the factors which influence vasomotor activity within the cotyledon, producing a minute-to-minute type of change?

Dawes. Yes. Fetal anoxemia caused by giving the mother low mixtures to breathe produces umbilical vasoconstriction in lambs of 140 days gestation, less frequently at 115 days, and not at all at 90 days. This vasoconstriction occurs in the umbilical arteries and veins and also between the cotyledonary arteries and veins, as evidenced by the changes in pressure and flow in the umbilical circulation.

My impression is that severe anoxemia is required to cause umbilical vasoconstriction. I do not know the mechanism, but it may be due to release of fetal catecholamines. We have not excluded the possibility that maternal catecholamines may cause vasoconstriction in the fetal villi. We have not examined the effect of fetal hypercapnia. The *direct* effect of lowered pO_2 or raised pCO_2 on the fetal villi has not been properly explored.

Pickering. A plot of placental and fetal weights at exact gestational ages reveals important interrelationships. The normal period of gestation in the Macaca mulatta monkey, in my colony, is 167 days, plus or minus 7 days (mean plus or minus standard deviation). The theoretical limit of the relationship of the rate of gain in body weight and placental weight is reached at exactly 167 days (fig. 31).

Dawes. Does the placental weight in the Rhesus monkey increase to a maximum before term?

PICKERING. Yes.

DAWES. Surely the crucial point is that in the Rhesus monkey the placenta grows much less rapidly during the last half of gestation, while the fetus continues to increase considerably in weight.

PICKERING. No. Actually, it is growing less rapidly, but so is the fetus. To my knowledge, these represent the only collected data on fetuses and

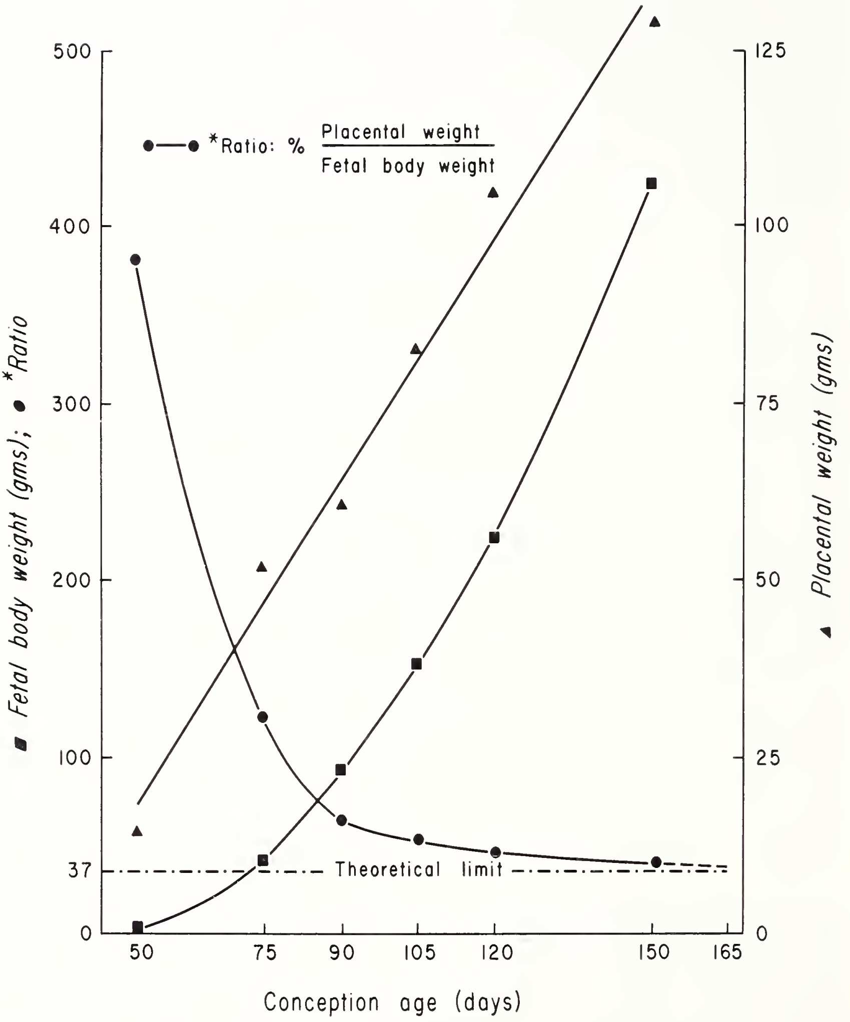

FIGURE 31.—Placental and fetal body weight in relation to conception age. (Reproduced by courtesy of Dr. D. E. Pickering, to be included in a monograph entitled "Skeletal Development in the Monkey," published by the University of Nevada Press, 1966.)

placentas of exactly known gestation from a healthy and standardized breeding colony.

BARRON. One constant cause of concern in all our studies on the physiology of fetal-maternal exchanges has been that the manipulations of the pregnant uterus and its contents—the delivery of the fetus by cesarean section, etc.—might so alter their physiology that our observations were not representative of steady-state unstressed conditions *in utero*.

Those of you who are familiar with the work of Sir Joseph Barcroft[9] will recognize this figure (fig. 32). I remember when these data were obtained under what I thought to be the best possible conditions. I think they could be easily duplicated in comparable conditions, that is, on fetal lambs delivered by cesarean section.

The oxygen saturation in the umbilical vein, as Sir Joseph pointed out, tends to rise to a maximum between 80 and 100 days gestation age and to decrease in a fairly regular manner until the end of term. In the umbilical artery, the saturation increases even more in the period 65 to about 100 days before it falls more or less parallel to that of the vein. In the final days just before delivery the saturation in the umbilical artery varies over a wider range.

In working with pregnant sheep, I have been impressed by the fact that the uterine musculature is relatively unresponsive to handling or manipulation between 60 and 100 days, but thereafter, as gestation advances, it

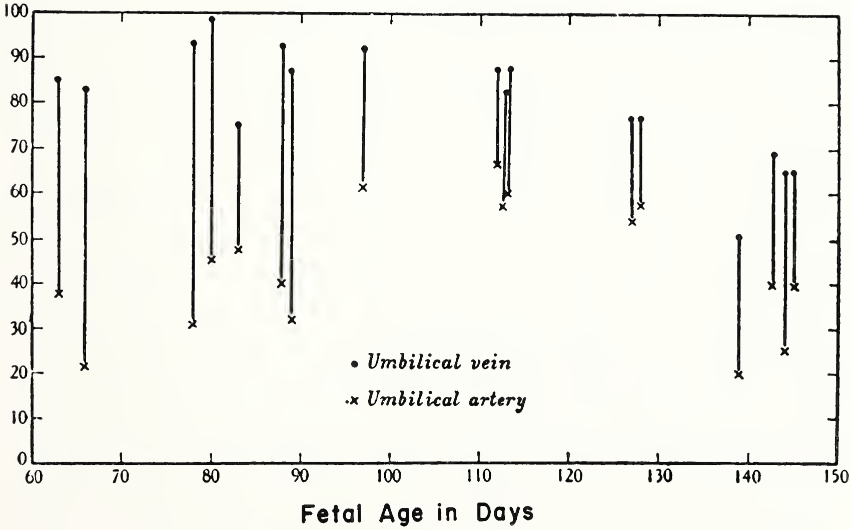

FIGURE 32.—Percentage saturation with oxygen of blood in umbilical vessels during fetal life. Reprinted, by permission, from Barcroft, J., Kennedy, J. A., and Mason, M. F.: Oxygen in the blood of the umbilical vessels of the sheep. *J Physiol 97: 347–356, 1940.*

becomes increasingly responsive—that is to say, it tends to contract more readily. This tendency probably increases in the smooth muscle of the vascular bed of the uterus and placenta as well; if it does, the regular changes in saturation Barcroft described might be due to a reaction of the placental vessels and not to any limitation of placental function normally present in the intact animal.

With this possibility in mind my colleagues and I have spent a great deal of time in recent years studying the circulation and blood gas levels on the two sides of the placenta in unstressed, unanesthetized animals in order to get some idea of the conditions that are compatible with the continued growth and development of the fetus. As one cannot judge the adequacy of a diet by the ingestion of a single meal, so one cannot judge the adequacy of any set of environmental conditions for fetal development from a single examination after which the fetus does not survive. Acute experiments on the uterine and umbilical circulation alone cannot provide data on the conditions essential for the continued fetal growth and development; the only test of their adequacy is fetal growth and survival.

What we felt was needed was a method for obtaining blood samples from the uterine and umbilical circulation without interrupting pregnancy, and to this end we have been developing methods for maintaining plastic catheters in the placental vessels. Our success with chronic catheters in maternal vessels encouraged us to try them in the umbilical vessels, and we are beginning to have some success with the maintenance of catheters on the fetal side of the placenta. With them we have followed the umbilical blood levels in fetal lambs over a period of a month without apparent interference with the normal intrauterine growth, birth, and postnatal development of the lamb. In some ewes we have had functional catheters in all four placental vessels for a week or 10 days, and in one we had three functional catheters for nearly a month.

Daily determinations of the oxygen capacity of the fetal blood sample via a catheter that ends in the free part of the umbilical cord indicate that it is fairly constant (fig. 33). Note the contrast between our results and those of Barcroft (fig. 34), in which the oxygen capacity of the fetal blood sampled after delivery by cesarean section with the cord attached, continued to rise as gestation advanced after the 100th day. Our data indicate that the oxygen capacity does not change if the ewe is free from stress. On the day following the operation at which the catheters were introduced the values tend to be higher. As the ewe recovers these values drop and then remain constant. We have followed the oxygen capacity of a kid prior to, during, and after delivery. It began to rise just prior to delivery, rose further during delivery, and reached a maximum after respiration was established.

Figure 35 illustrates some of the values for oxygen saturation we have obtained in sheep. In contrast to the results of Barcroft and his associates

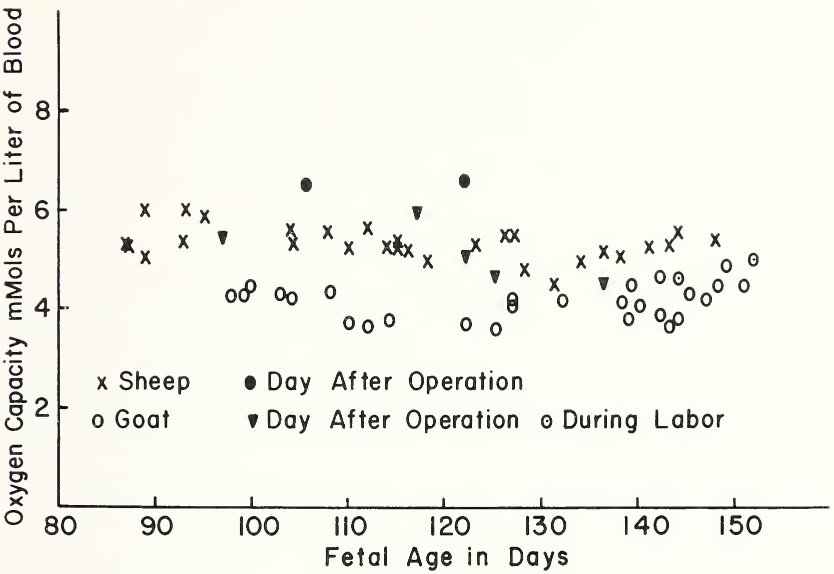

Figure 33.—The oxygen capacity of the fetal blood is plotted against age in days. Reprinted, by permission, from Meschia, G., Cotter, J. R., Breathnach, C. S., and Barron, D. H.: The hemoglobin, oxygen, carbon dioxide and hydrogen ion concentration in the umbilical bloods of sheep and goats as sampled via indwelling plastic catheters. *Quart J Exp Physiol 50: 185–195 (Apr) 1965.*

(fig. 32) there is no regular change as gestation advances. Figure 36 illustrates the oxygen pressures in the umbilical vein and umbilical artery, respectively. Here, too, the values for the bloods in the two vessels vary over a narrow range without any tendency to change with advancing gestation. We can predict the onset of labor by following the oxygen capacity. If the oxygen capacity rises, there is a high probability that the lamb or kid will be delivered within 24 hours.

To return to the question: Does the functional capacity of the placenta as an organ of gas transfer keep pace with the needs of the fetus as gestation advances or does it fall behind? We have been concerned with just how to assess the functional capacity of the placenta—the estimation of its diffusing capacity for oxygen is technically difficult. To acquire the necessary technical skills, it seemed worthwhile first to study quantitatively the placental transfer of urea, a small and relatively inert molecule. We made use of our animal preparation in which a catheter is introduced into each of the four placental vessels.

Urea was infused into the maternal circulation for 7 minutes to establish a concentration gradient between the uteroplacental and umbilical bloods. The concentration changes in each of the four placental vessels were followed by analyses of blood samples drawn at selected intervals after the beginning

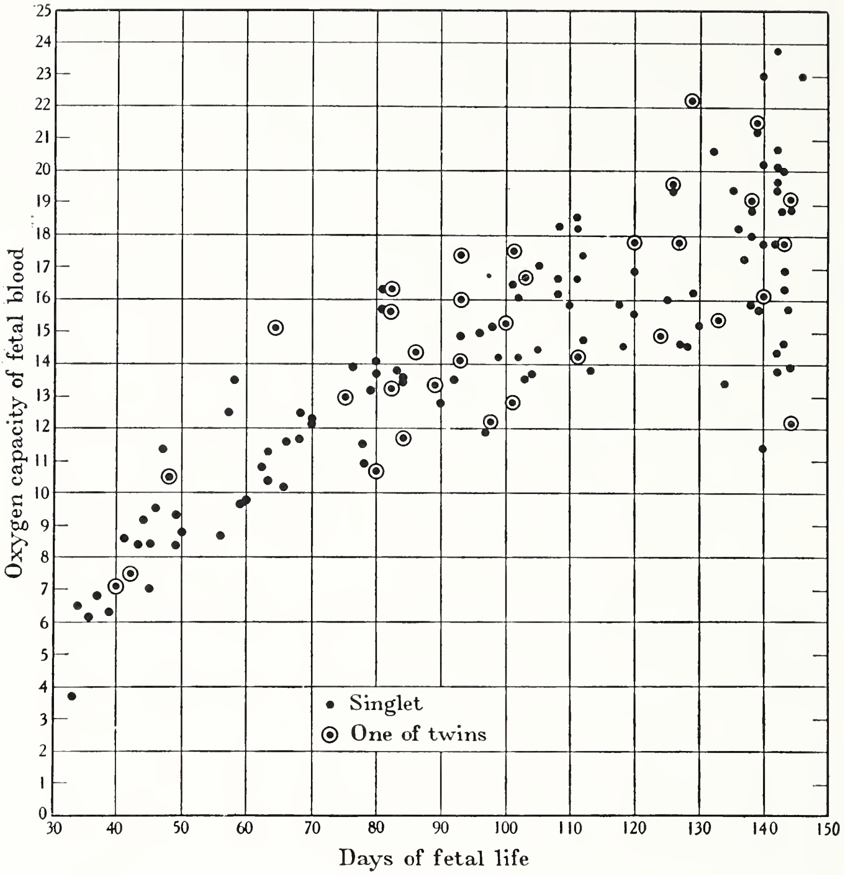

FIGURE 34.—Oxygen capacities of fetuses from Welsh ewes at successive ages. Reprinted, by permission, from Barcroft, J.: *Researches in Prenatal Life.* Oxford, Blackwell Scientific Publications, 1947, 292 pp.

of the injection over a 30-minute period. From these values, the average difference in urea concentration on the two sides of the placenta during the 30-minute period was calculated and the total amount transferred in that interval was determined by analysis of the fetal carcass. With these data, obtained on ewes between 90 days gestation and term, we have estimated the "diffusing capacity" of the placenta for urea, the quantity transferred per minute per unit difference in concentration on the two sides, and we have related this to the weight of the fetus it served.

Figure 37 illustrates the results we obtained, and the fact that there appears to be a fairly linear relationship between the permeability of the placenta to urea—as expressed by the "diffusing capacity"—and the weight of the fetus.

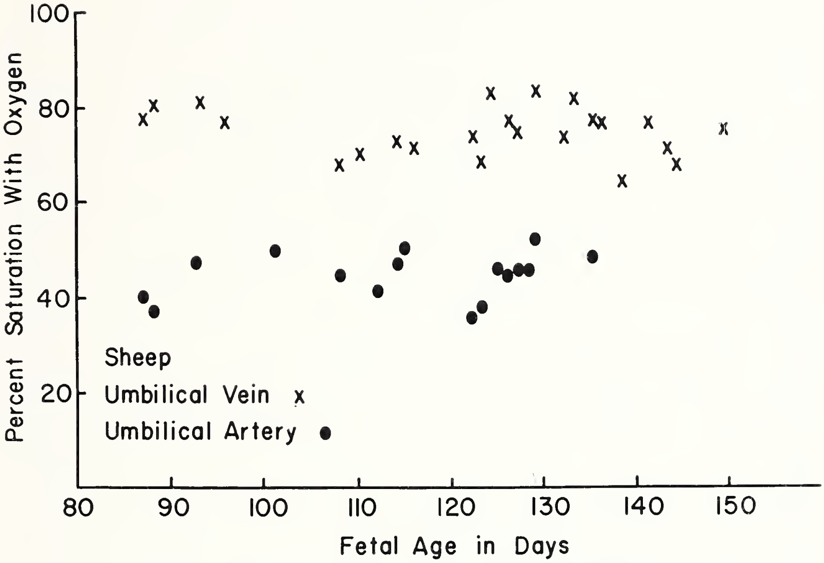

FIGURE 35.—The percentage saturation of the umbilical arterial and venous bloods, respectively, of the fetal lamb, is related to gestation age. Reprinted, by permission, from Meschia, G., Cotter, J. R., Breathnach, C. S., and Barron, D. H: The hemoglobin, oxygen, carbon dioxide and hydrogen ion concentrations in the umbilical bloods of sheep and goats as sampled via indwelling plastic catheters. *Quart J Exp Physiol 50: 185–195 (Apr) 1965.*

The sheep placenta reaches its maximum weight at about 100 to 110 days—full term circa 147—so it is clear that weight cannnot be used as an index of the functional capacity of the placenta.

In the absence of evidence to the contrary, it seems reasonable to conclude that the capillaries on the two vascular nets of the placenta—fetal and maternal—are not effectively restricting the diffusion urea. If the placental capillaries are like the capillaries elsewhere in the body, we might expect that urea would cross them very rapidly. If that is the case, the only element left to offer selective permeability is the trophoblast. I offer it as a suggestion—nothing more—that what we have measured is the increase in the surface area of the trophoblast with advancing gestation; that is, the growth of that particular component of the placenta which is concerned with the active transport of materials.

VILLEE. Dr. Barron, I think it is interesting that your data, in conjunction with Dr. Pickering's figures about placental weight, show that one cannot infer that any aspect of placental physiology is maximal just because the weight of the placenta is at its maximum.

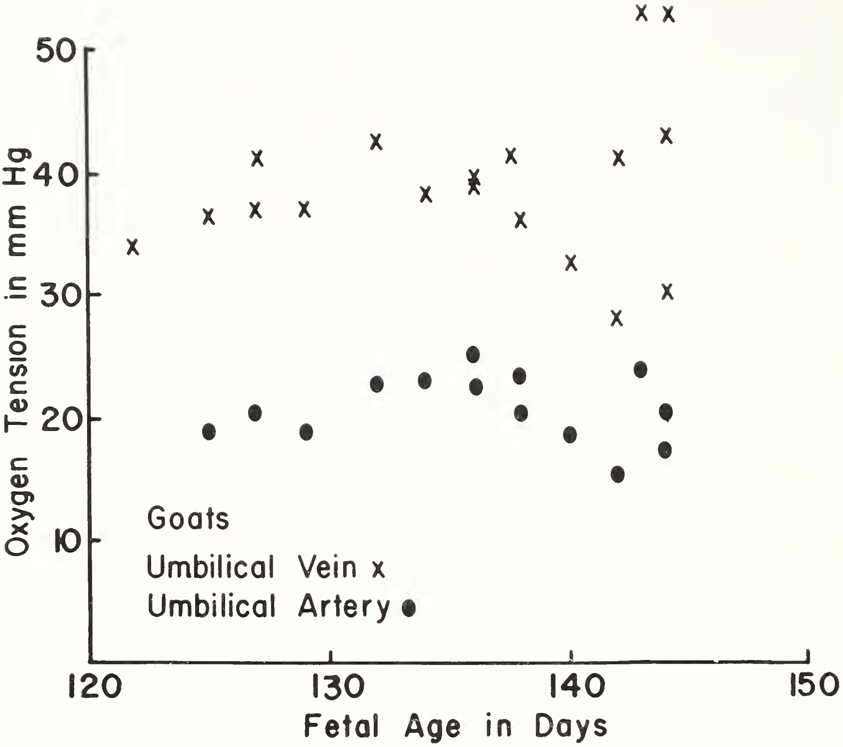

FIGURE 36.—Oxygen pressures in the umbilical vein and umbilical artery, respectively.

BARRON. I won't go into details, but such data as we have on the "diffusing capacity" of the placenta for oxygen and nitrous oxide in some of these same animals on which we have data for urea suggest that the transfer of these gases is not limited by the trophoblast but by the blood flow through the two vascular nets of the placenta. By means of indwelling catheters, we propose to investigate this possibility further and ultimately to learn how uteroplacental function in the intact unstressed ewe differs from that observed after delivery of the fetus by cesarean section.

VILLEE. There is a long history of discussion on whether the oxygen supply to the fetus is less than that in the adult, and whether it is in some way limiting to the growth and development of the fetus. It was reassuring to hear from Dr. Barron that the oxygen supply to the sheep fetus, when the maternal sheep is conscious and walking around in the field, is relatively constant throughout gestation. There had been some concern that the fetus is characterized by some peculiar kind of metabolic pathway, or system of metabolism, by which it could survive and grow despite a lower oxygen tension in its tissues. There appears to be ample evidence for quantitative differences between the types of metabolism in fetal and adult tissues but

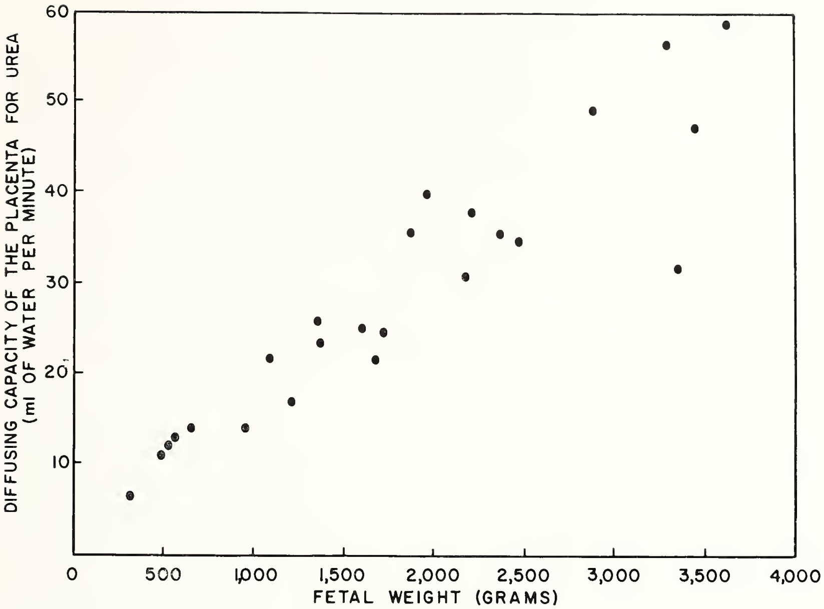

FIGURE 37.—Permeability of the placenta to urea. Reprinted, by permission, from Meschia, G., et al: The diffusibility of urea across the sheep placenta in the last two months of gestation. *Quart J Exp Physiol 50: 23–41 (Jan) 1965.*

no clear evidence for qualitative differences. There is no metabolic pathway that occurs in fetal tissue that cannot to some degree be found in adult tissue.

There is the general question of when, in the course of development, do tissues acquire their adult capabilities? This question applies not only to the fetal lung, which is of primary concern to this conference, but to all fetal tissues. There are some enzymes that change abruptly in their activity just at the time of birth, but many others do not undergo such changes. Their activity gradually increases throughout development, or they attain an adult level of activity at a very early time in development and remain essentially unchanged after that.

FREMONT-SMITH. Are you indicating that a particular enzyme changes function, or that there is a relative change of proportion?

VILLEE. There is no change in the function of an enzyme, but there is a change in its amount or in its activity. The enzyme activity is measured and found to increase sharply just before or just after birth. The factors that may control this abrupt change in enzyme activity are of considerable interest at the moment in view of our current theory regarding the control of protein synthesis via DNA and RNA.

EFFECTS OF UTERINE PRESSURE ON THE FETUS

Caldeyro-Barcia. The research was done in Rhesus monkeys and in human beings. To study the effect of uterine contractions on the fetus, we recorded the fetal heart rate (FHR) and, in some cases, the fetal pO_2. To record the fetal electrocardiogram without interference from the maternal side, a very thin electrode (0.5 mm diameter) was inserted into the muscles of the fetal buttock. The electrode, ending in a hook, was threaded through a No. 20 gauge needle. After the puncture was made, the needle was withdrawn and only the electrode remained inserted. The fetal electrocardiogram obtained by this method permitted the accurate study of the characteristics of the waves, segments, and QRS complex.

A similar method was employed for inserting a polarographic electrode to obtain the record of fetal pO_2. The placenta was first located radiographically, in order to avoid its puncture. The other electrodes were placed on the skin of the maternal abdomen. After rupture of the membranes, a second electrode was inserted under the fetal scalp. This head-buttock lead has been designated F_1 at our laboratory by Poseiro and Figueroa.[10]

Since the amplitude of the fetal ECG is much greater than that of the maternal, it is easy to feed a tachometer with the largest wave of the fetal ECG and obtain a continuous tracing of the FHR, beat-to-beat, without interference from the maternal ECG. At the same time, the catheter placed in the amniotic fluid cavity gives a simultaneous record of uterine contractions (fig. 38). The correlation between the changes in amniotic pressure and those in the FHR is the goal of our study.

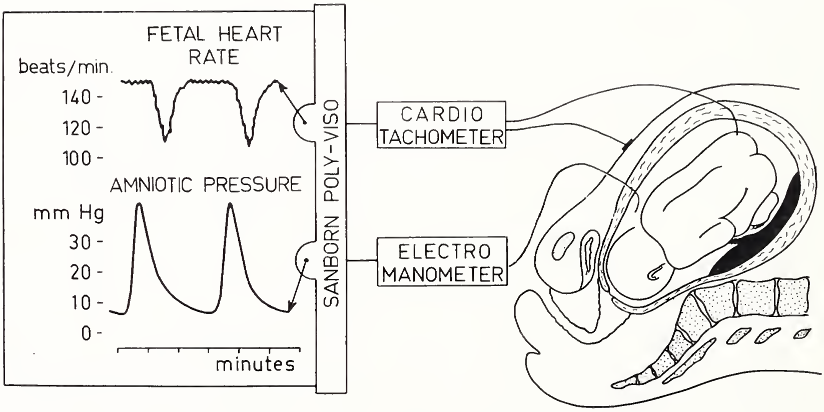

Figure 38.—Method employed for the simultaneous recording of uterine contractions and fetal heart rate (FHR). The cardiotachometer is fed by the fetal ECG which is obtained with a thin electrode inserted under the skin of the fetal buttock.

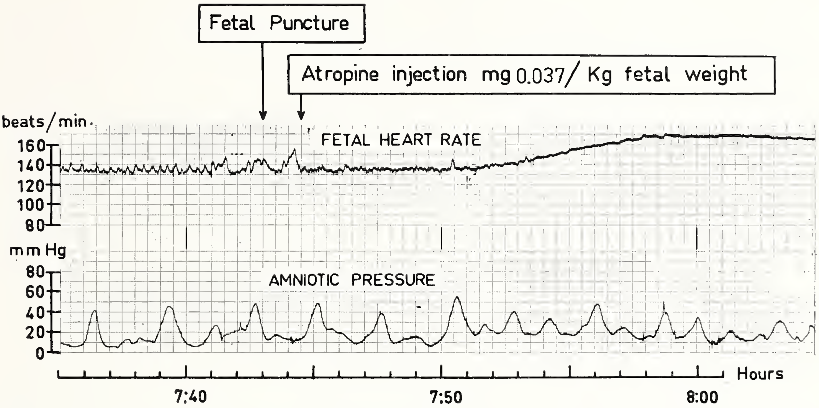

Figure 39.—Simultaneous recording of fetal heart rate (FHR) and amniotic fluid pressure in a multipara who, in the 39th week of pregnancy, started labor spontaneously. At the time of the injection of atropine, the dilatation of the cervix had progressed to 4 cm; the membranes were intact and the head was in L.O.T. and station —3. The spontaneous uterine contractions have characteristics which are within the normal range for early first stage of labor; they did not produce "dips" in FHR tracing which showed the characteristic "rhythmic oscillations." The puncture of the fetus caused an immediate and transient rise in FHR; the injection *per se* had a similar, independent effect. The actual pharmacologic effects of atropine on FHR started 7 minutes after the injection, involving the slow rise of basal FHR and the suppression of the "rhythmic oscillations." Forceps delivery at hour 13:45, the Apgar score being 10. Reprinted, by permission, from Méndez-Bauer, C., et al: Effects of atropine on the heart rate of the human fetus during labor. *Amer J Obstet Gynec 85: 1033–1053, 1963* (The C. V. Mosby Co., publishers).

Figure 39 shows a tracing obtained in a normal labor. The membranes were intact and cervical dilatation was 4 cm. In these conditions, normal uterine contractions should not produce any changes in the FHR. These are small oscillations, about 3 to 5 per minute, which are present in normal FHR tracings. These oscillations indicate rhythmic, cyclic changes in the vagal tone. Their vagal nature is shown by the effects of atropine injected into the fetal buttock. The oscillations disappear 5 to 10 minutes after the injection. At the same time, the FHR increases from 135 to 168 beats per minute; this change in the FHR may be taken as an indirect measure of the vagal tone.

Avery. How large are the fluctuations in fetal heart rate?

Caldeyro-Barcia. Usually the amplitude of the rhythmic oscillations ranges from 3 to 6 beats per minute. In figure 39 the average amplitude is about 8 beats per minute.

Avery. Are they always present?

Caldeyro-Barcia. Yes. They have also been detected by Swartwout and associates [11] in different stages of pregnancy. We have found them in almost every normal fetus; they were absent in four anencephalic fetuses. There is some cyclic mechanism in the central nervous system which acts on the center of the vagus nerve and produces these rhythmic changes. One possible explanation is a cyclic activity of the respiratory center of the fetus. Their slow frequency (3 to 5 per minute) would agree with the participation of the respiratory center. The discharges of the respiratory center would not be strong enough to expand the lungs but would be strong enough to influence the vagus center. This is only one of the many possible explanations.

James. How high does the rate rise with atropine?

Caldeyro-Barcia. The rate in this particular case rose to 168 beats per minute. Before atropine, the average FHR between peaks and valleys of these oscillations was 135 beats per minute. Usually the frequency of the oscillations ranges from 3 to 5 per minute, but it may change very much. During fetal asphyxia, the oscillations increase in amplitude and frequency. They are not perceived by clinical auscultation, because the change in frequency is very small. When they are of a greater amplitude, however, they may be perceived clinically as irregularities in the heart rhythm.

Under certain conditions, uterine contractions cause transient falls in the FHR which are designated as "dips." The term "dip" is preferred to "bradycardia" since it gives a better idea of a transient drop followed by complete recovery, and because in many dips the FHR does not reach "bradycardic" levels (below 120 beats per minute). The FHR recorded between the dips is designated as *Basal FHR* (fig. 40). The *amplitude* of each dip is the difference existing between the *Basal FHR* preceding the dip, and the *Minimal FHR* which is recorded at the bottom of the dip. The *Minimal FHR* is measured at the mean value between peaks and valleys of the rhythmic oscillations recorded at the bottom of the dip.

The *duration* of the dip is the time (measured in seconds) during which the fetal heart rate remains below a certain level; for the purpose of analysis this level has been set at 6 beats per minute below the *Basal FHR* preceding the dip.

The *lag time* is the interval (measured in seconds) elapsing from the peak of the contractions to the bottom of the corresponding dip. The dips may be classified into two types according to the lag time between contraction and dip.

The frequency distribution for the values of the lag time can readily be divided into two groups depending upon the obstetrical conditions: group I is made up of values obtained in four subjects following rupture of the membranes, and when cervical dilatation was between 5 and 10 cm; group II consists of values obtained when cervical dilatation was between 2 and 5

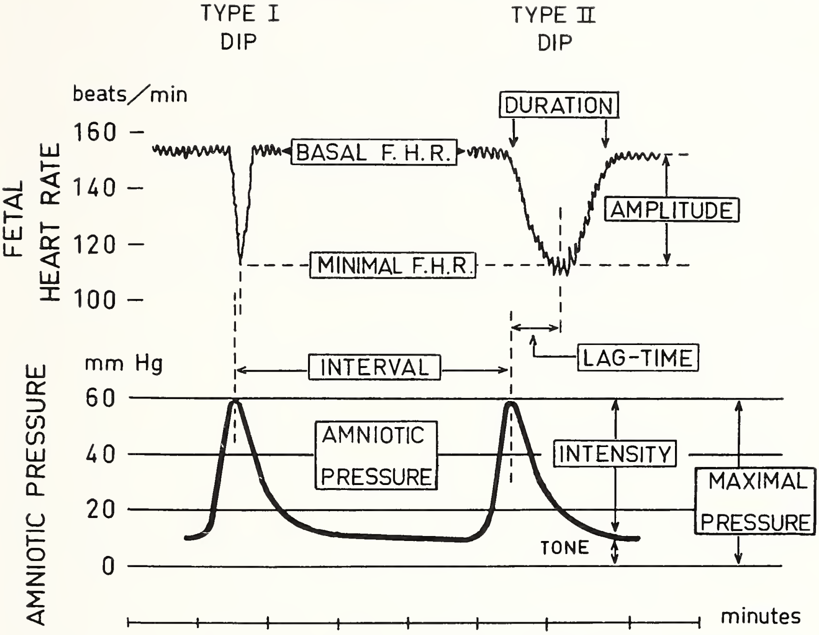

Figure 40.—Diagram illustrating the parameters analyzed in the tracings of fetal heart rate (FHR) and amniotic fluid pressure and their chronological relationship. Reprinted, by permission, from Méndez-Bauer, C., et al: Effects of atropine on the heart rate of the human fetus during labor. *Amer J Obstet Gynec 85: 1033–1053, 1963* (The C. V. Mosby Co., publishers).

cm. The membranes were intact in six of these subjects, and ruptured in one (#1500). Figure 41 shows the mean frequency distribution of groups I and II. The differences between the mean of both samples is highly significant ($p<0.0001$).

Based on this difference, we propose to classify the dips into two types according to the value of the lag time. The limits are tentative and will be adjusted as more samples are analyzed. Tentatively, a dip will be classified as belonging to Type I when its lag time is between -11 and $+16$ seconds, and to Type II when its lag time is between $+23$ and $+67$ seconds. If the lag time falls outside these two ranges, the dip will be considered as unclassified.

Ramsey. Is there a certain interval between the start of the contraction and the onset of the Type I dip? Is this constant?

Caldeyro-Barcia. No.

Ramsey. Is there a threshold of pressure at which the dip commences?

Caldeyro-Barcia. This threshold varies, depending on many conditions. We have studied many parameters. The chronological relationship which has proved more useful to classify dips into Types I and II is the lag time

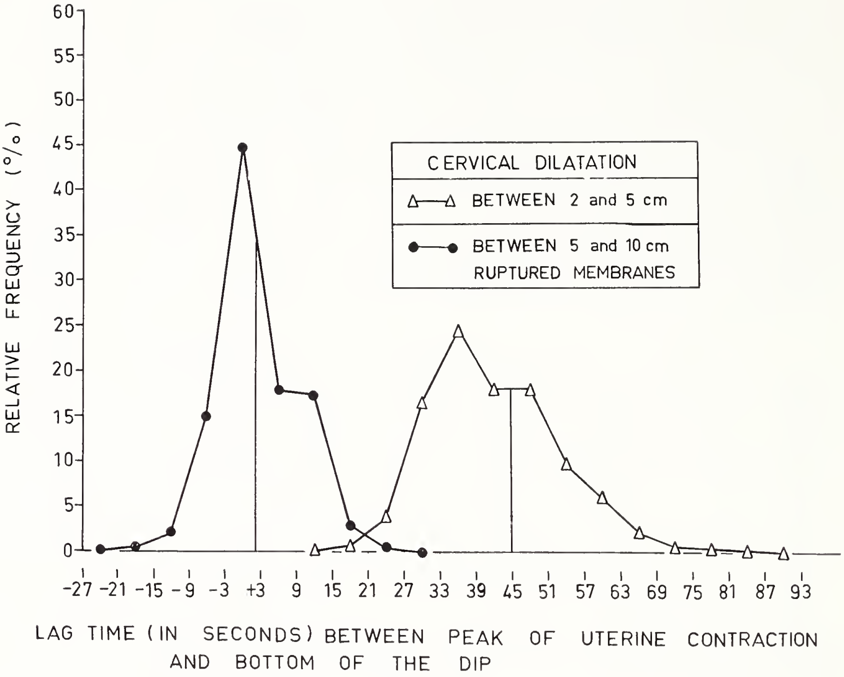

Figure 41.—Frequency distribution of the values for the lag time. The frequency polygon on the left corresponds to sample I, obtained in four labors with ruptured membranes and cervical dilatation between 5 and 10 cm. The polygon on the right corresponds to sample II obtained in seven labors with cervical dilatation between 2 and 5 cm. The difference between the means of both samples is highly significant. Reprinted, by permission, from Althabe, O., et al: Effects of uterine contractions on fetal heart rate. To be published.

between the peak of the contraction and the bottom of the dip. In Type I dips the average lag time is only 2.5 seconds; in Type II dips, the average value is 45 seconds.

Figure 42 illustrates schematically the principal graphic characteristics of both types of dips, including their relationship with the corresponding uterine contraction, and is based on statistical analysis of 954 dips recorded in 14 labors.

The amplitude of the dips does not permit differentiation of Type I from Type II. In both types the amplitude may be small (less than 20 beats per minute), medium (from 20 to 40 beats per minute), large (40 to 60 beats per minute), or very large (more than 60 beats per minute). For a similar amplitude, Type I dips usually have a shorter duration (and a more acute angle) than Type II dips (compare figs. 43 and 44). However, neither the duration nor the angle *per se* permits the diagnosis of the type of dip, since there is great overlapping between the values corresponding to Type I and Type II dips.

For a similar amplitude, the slope of the descending and the ascending limbs of Type I dips is usually greater than that of Type II dips. The slope of the limbs in Type I dips increases with the amplitude, and the angle consequently becomes more acute. A similar, though less evident, relation has been found between amplitude, angle, and slope for Type II dips. In

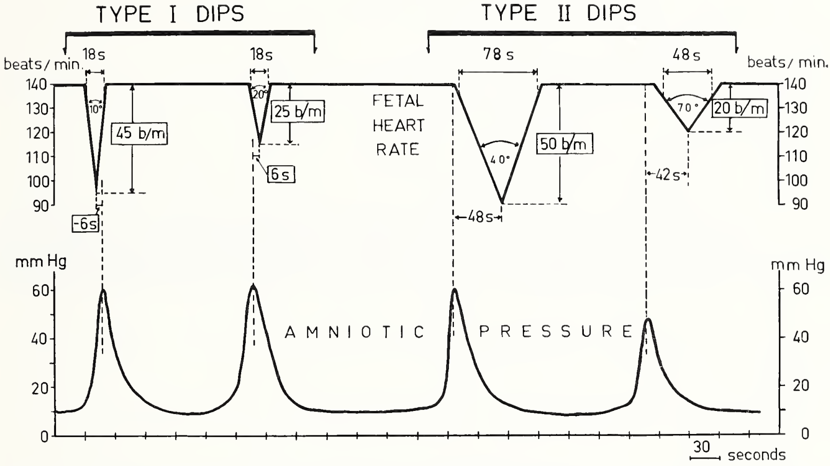

FIGURE 42.—Scheme illustrating the principal characteristics of Type I and Type II dips in FHR tracings. Reprinted, by permission, from Beauquis, A., et al: Quantitative study of the dips produced in fetal heart rate by uterine contractions. To be published.

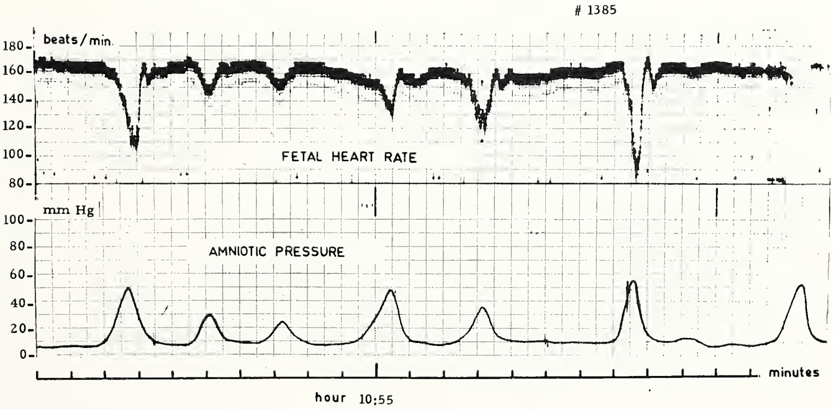

FIGURE 43.—Type I dips recorded at slow paper speed. Cervical dilatation 8 cm. Ruptured membranes. L.O.A. in —2 station. Loop of the cord around the fetal body. Apgar score 10.

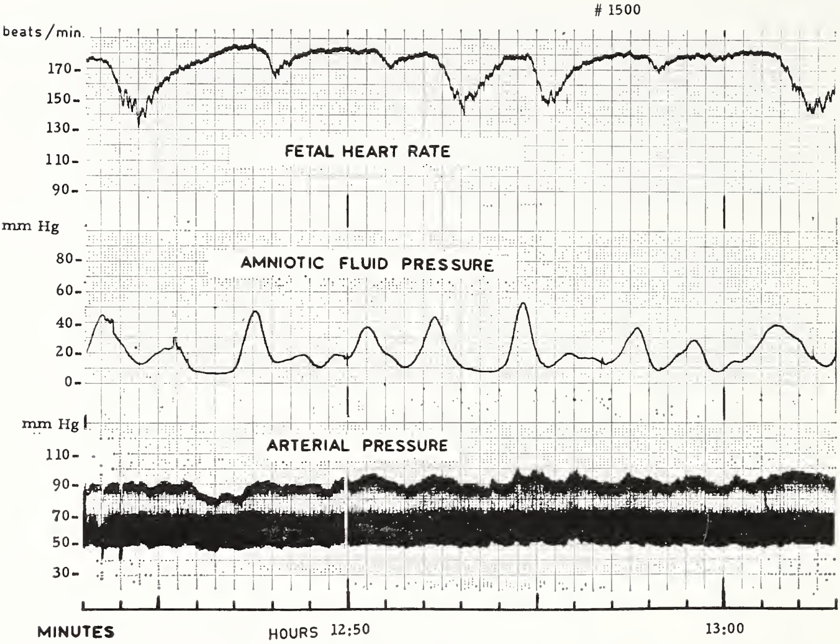

Figure 44.—Type II dips recorded at slow paper speed. Cervical dilatation 3 cm. L.O.T. in —3 station. Normal uterine contractions induced with oxytocin at 8 milliunits/min. Loop of the cord around the fetal neck. Arterial hypotension of the mother. Delivery 6 hours later. Weight of the newborn 5 kg. Apgar score 3.

Type II dips, the duration bears a positive correlation with the amplitude (fig. 42). In Type I dips, a similar correlation is present only in a few labors. The majority of cases show no correlation between amplitude and duration.

The shape is not a reliable criterion for classifying the dips into Type I and Type II. For example, all the dips shown in figure 43 belong to Type I, since their lag time is much shorter than 16 seconds; however, some dips are V-shaped whereas others are U-shaped. The change in shape depends, among other factors, on the amplitude of the dip as well as on the speed of the recording paper.

Dips can be perceived by clinical auscultation. The perception of Type I dips is hindered by the fact that these dips are produced at the acme of uterine contractions, when extreme tenseness of the myometrium makes it very difficult to hear the fetal heart tones. Type I dips, if heard, are perceived as a rapid fall of the FHR, with a short duration and rapid recovery. There is no need to actually count the FHR, since the change in rate is easily appreciated because of the great velocity of the variation. Furthermore, the short duration of the dips makes it very difficult to estimate the actual value of these changes.

To clinically perceive Type II dips, it is necessary to count the FHR during several consecutive periods of 10 seconds each. The rate corresponding to each period should be noted. The count should begin before the uterine contraction reaches its peak and must continue for at least 1 minute after the uterus is fully relaxed. Type II dips are perceived as a slow fall in rate which starts after the peak of the contraction and reaches minimum values about 30 to 50 seconds later, that is, when the uterus is fully relaxed. The recovery of the FHR to its initial value is also slow and takes about the same time as the fall. In Type II dips the changes in FHR are slow and may not be perceived without actually counting and noting the rate every 10 seconds. Any perceived drop of more than 15 beats per minute following the acme of the contraction, and having the chronological pattern just described, should be considered a Type II dip. For example, if the heart rate before the contraction was 155 beats per minute, and after the contraction the rate fell transiently to 125 beats per minute, it should be considered a Type II dip with an amplitude of 30 beats per minute. These variations of FHR following each uterine contraction are a sign of fetal distress, even though the absolute value of the FHR is always within the "normal" range (120 to 160 beats per minute).

The rhythmic oscillations of the FHR are not usually perceived clinically when their amplitude is less than 10 beats per minute. When the amplitude of the rhythmic oscillations surpasses 10 beats per minute they are perceived clinically as irregularities in the heart rhythm.

Simultaneous recording of the amniotic pressure and the partial oxygen pressure (pO_2) in fetal tissues shows that each uterine contraction causes a slow and transient fall of fetal pO_2. The bottom of the pO_2 fall is recorded about 30 to 45 seconds after the peak of the contraction, that is, a lag time similar to that of Type II dips.

Figure 45 illustrates the record of fetal muscular pO_2 ($FMpO_2$) obtained with a polarographic electrode inserted into the buttock muscle of a human (anencephalic) fetus. Each uterine contraction causes a marked fall of $FMpO_2$. The onset of this fall is recorded a few seconds after the onset of the contraction. The bottom of the fall of $FMpO_2$ occurred 30 to 45 seconds after the peak of the contraction. (The record of the FHR has been omitted in figure 45 because prior to hour 15:10 it was unreliable due to failure of the cardiotachometer.) Figure 46 shows the histogram for the values of the lag time between the peak of the contraction and the bottom of the $FMpO_2$ fall. These values have a frequency distribution similar to that for the lag time of Type II dips. Type I dips do not cause a fall in $FMpO_2$.

The recovery of $FMpO_2$ is very slow and takes 2 to 5 minutes to reach its initial level. This slow recovery could be explained by vasoconstriction in the skeletal muscles (and perhaps the skin and other peripheral areas)

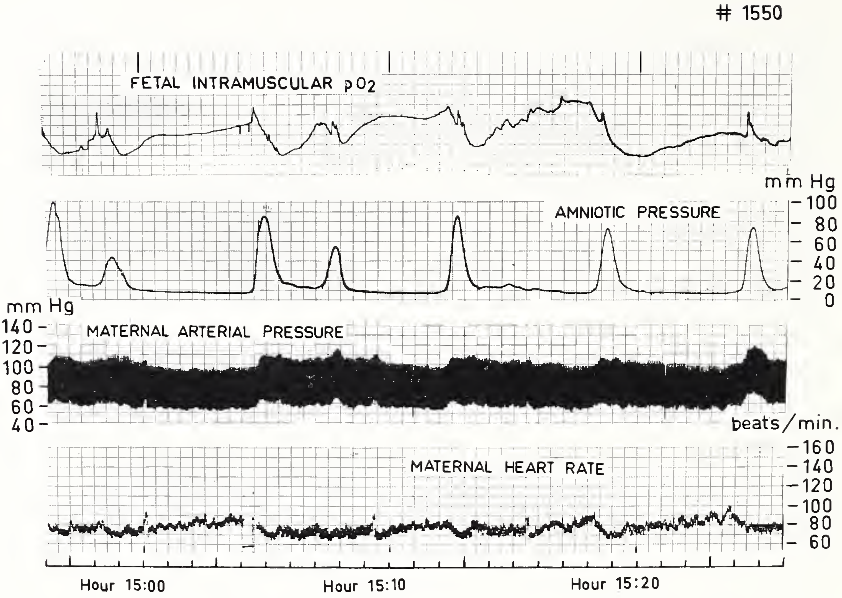

Figure 45.—Anencephalic fetus. Record obtained at the 37th week of pregnancy. Acute polyhydramnios. Labor had been induced by the withdrawal of 6 liters of amniotic fluid. At hour 15 cervical dilatation was 4 cm, and membranes were intact. The record of fetal muscular pO_2 ($FMpO_2$) was obtained with a polarographic electrode inserted into the buttock muscle of the fetus. Each uterine contraction causes a marked fall of $FMpO_2$. The onset of this fall is recorded a few seconds after the onset of the contraction. The bottom of the fall of $FMpO_2$ occurred 30 to 45 seconds after the peak of the contraction (see fig. 46). The recovery of $FMpO_2$ after each fall is very slow and takes 2 to 5 minutes to reach its initial level. Reprinted, by permission, from Pose, S. V., Escarcena, L., and Caldeyro-Barcia, R.: Effects of uterine contractions on the pO_2 of the human fetus. To be published.

due to an increase in the fetal sympathetic tone elicted by the hypoxia. The administration of pure oxygen to the mother causes a rise in the pO_2 of fetal tissues. When the fetal pO_2 rises above a certain "critical value," uterine contractions no longer cause Type II dips (fig. 47). When fetal pO_2 descends below the "critical" level, a remarkable parallelism has been found between the tracings of fetal pO_2 and FHR.

A working hypothesis can be postulated for the mechanism producing Type II dips (fig. 48). Uterine contraction causes a transient fall in fetal pO_2 (fetal hypoxia) which in turn causes the Type II dips in FHR. Uterine contractions cause the transient fall in fetal pO_2 according to the following mechanisms:

(*a*) Reduction of fetal blood flow through the placental chorionic villi as a result of compression of the umbilical cord by uterine contractions.

(*b*) Reduction of maternal blood flow through the intervillous space. This effect may be accomplished by uterine contractions in two ways:

(1) Compression of the intramyometrial aspect of the vessels supplying the intervillous space.

(2) Compression of the retrouterine segment of the aorta or iliac arteries with a consequent drop of arterial pressure in the pelvis and lower limbs (Poseiro effect).

As a result of any of these mechanisms, the fetal pO_2 falls slowly as the available oxygen is consumed by the fetus. This slow fall of pO_2 is in keeping with the slow fall of the FHR and the prolonged lag time between the peak of the uterine contraction and the bottom of the Type II dip.

The transient fall in fetal pO_2 causes the Type II dip by at least two mechanisms, one vagal and the other extravagal. Both mechanisms act simultaneously, and their depressing effects on the FHR are additive.

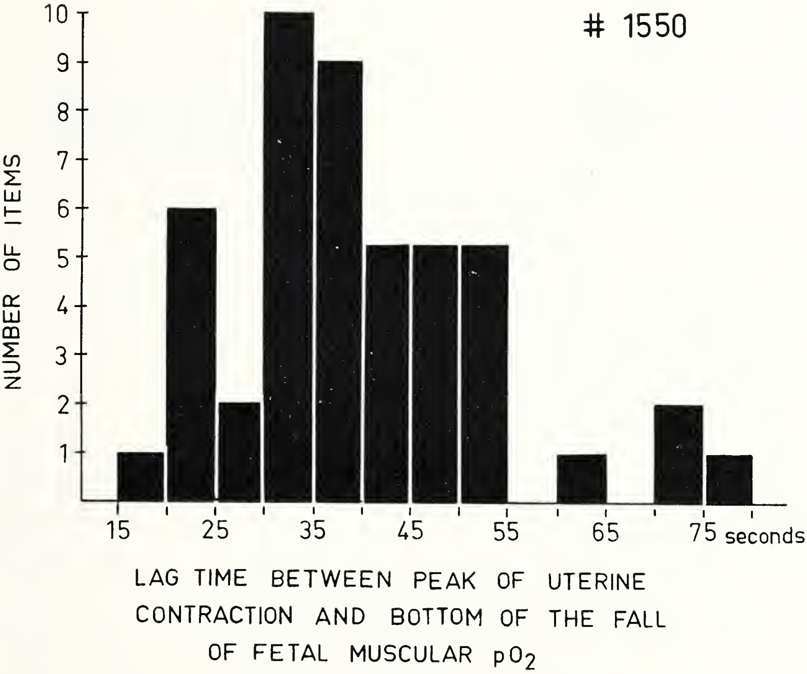

FIGURE 46.—Histogram for the values of the lag time between peak of the contraction and bottom of the $FMpO_2$ fall measured in experiment No. 1550 (see fig. 45). These values have a frequency distribution similar to that for the lag time between peak of contraction and bottom of Type II dip, as illustrated in figure 41. This agreement further supports the hypothesis illustrated in figure 48 concerning the hypoxic mechanism of Type II dips. Reprinted, by permission, from Pose, S. V., Escarcena, L., and Caldeyro-Barcia, R.: Effects of uterine contractions on the pO_2 of the human fetus. To be published.

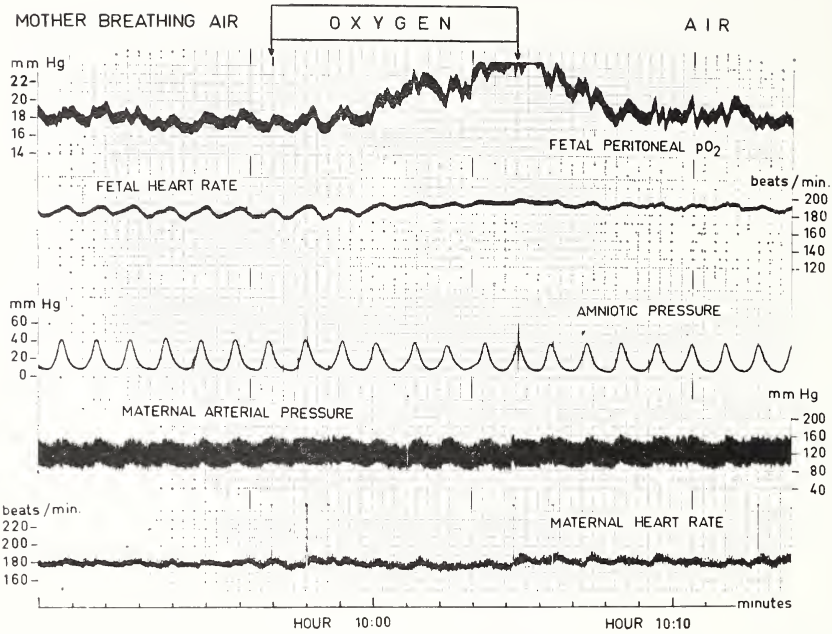

Figure 47.—When the mother breathes air, each uterine contraction causes a Type II dip in fetal heart rate (FHR) and parallel drop of fetal peritoneal pO_2 ($FPpO_2$). The administration of pure O_2 causes a slow rise in $FPpO_2$ (from 16–18 mm Hg to 24 mm Hg); the basal FHR also rises, and Type II dips almost disappear. When the mother resumes breathing air, the records progressively recover their initial characteristics. Record obtained in a full-term pregnant Rhesus monkey. Uterine contractions induced with infusion of oxytocin at the rate of 1 milliunit/kg/min. Reprinted, by permission, from Pose, S. V., Escarcena, L., Behrman, R., and Caldeyro-Barcia, R.: Effects of uterine contractions on fetal pO_2 and heart rate in the Rhesus monkey. To be published.

(*a*) *Vagal mechanism.*—Hypoxia stimulates the center of the vagus by a direct effect and also, reflexly, by stimulating the carotid chemoreceptors. The resulting rise in vagal tonus causes the fall in FHR. This vagal mechanism may be blocked by giving parasympatholytic drugs (e.g., atropine) to the fetus.

(*b*) *Extravagal mechanism.*—Hypoxia, acting directly on the heart, depresses its automatism and causes a fall of the FHR. This mechanism should not be influenced by the administration of atropine to the fetus, since it does not involve the vagus nerve.

The coexistence of the vagal and extravagal mechanisms is supported by the effects of atropine on Type II dips. In figure 49, before atropine administration, uterine contractions caused Type II dips of large amplitude. After atropine administration, the amplitude diminished markedly. The dips, however, do not disappear completely as is the case with Type I dips. The

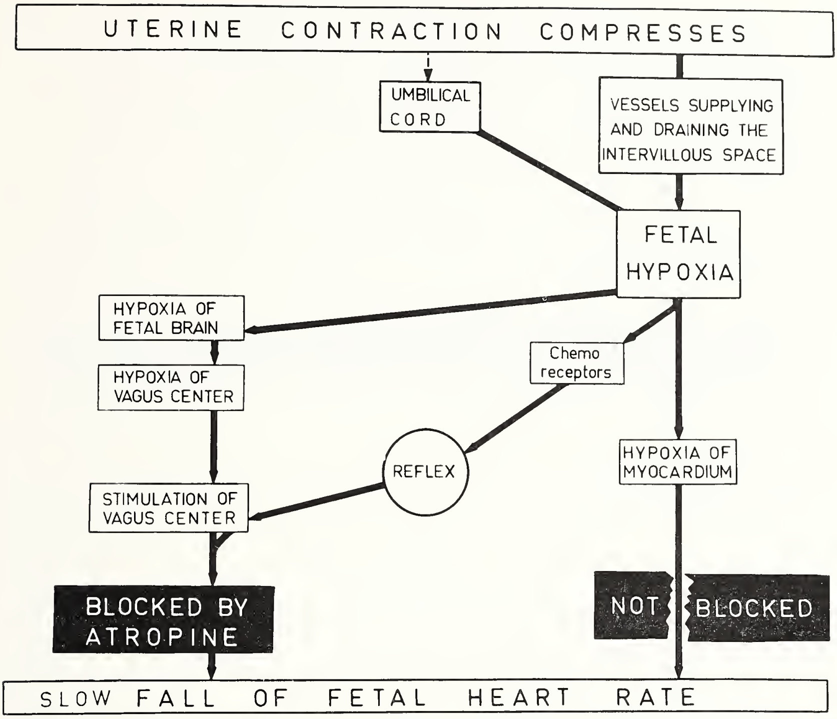

FIGURE 48.—Scheme illustrating the working hypotheses postulated for explaining the mechanisms of Type II dips. Reprinted and modified, by permission, from Méndez-Bauer, C., et al: Effects of atropine on the heart rate of the human fetus during labor. *Amer J Obstet Gynec 85: 1033–1053, 1963* (The C. V. Mosby Co., publishers).

duration and the lag time of Type II dips were not affected by atropine. Atropine blocks the vagal effect on the heart, thus diminishing the amplitude of Type II dips. They do not disappear completely, however, because the extravagal mechanism, which is not affected by atropine, continues to act after the injection of the drug.[12]

VILLEE. One of the things that struck me was that the Type II dip follows the peak of the contraction by 40 seconds in the monkey, apparently just as it does in the human. Would you comment on this?

CALDEYRO-BARCIA. The average lag time of Type II dips was similar in monkeys and in human beings. The lag time is a very consistent parameter. For example, after atropine, Type II dips become much smaller but the lag time remains the same.

COOK. It is surprising that the inhalation of oxygen would have this effect. If the mother is normal and breathing air at the time she is having the Type II dips, there should not be much increase in the oxygen content of the blood

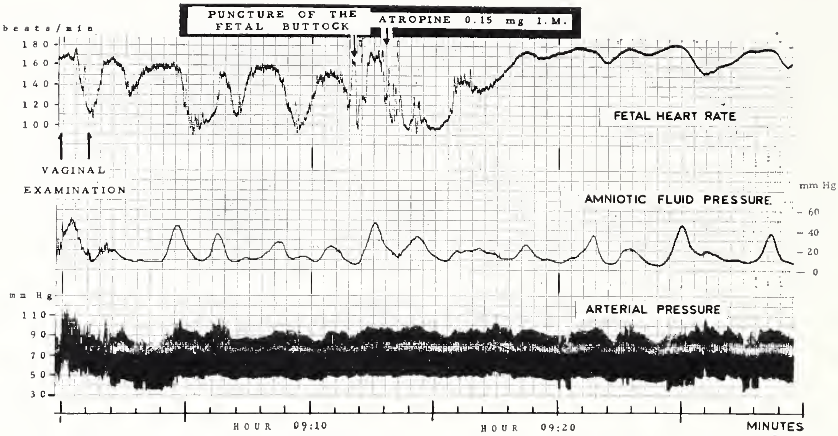

Figure 49.—Before atropine, uterine contractions of medium intensity caused Type II dips of great amplitude. The very strong effects of contractions on fetal heart rate (FHR) may be in relation with the loop of the cord around the neck and with the maternal arterial hypotension induced by the infusion of meperidine hydrochloride (Demerol) and chlorpromazine. After atropine was injected to the fetus, basal FHR increased, and the amplitude of the dips was reduced to about 40 percent of their initial value. No changes occurred in the duration of the dips or in the lag time between contraction and dip. The rapid oscillations superimposed on basal FHR and on the dips were completely suppressed by atropine. The dose of atropine was 0.03 mg per kg of fetal weight (5 kg). The record was obtained in a multipara at the 40th week of pregnancy in which labor was induced by intravenous infusion of oxytocin at the rate of 8 milliunits/min. Cervical dilatation had progressed to 3 cm, and the head was in O.L.T., station —4. The woman was in supine position. Reprinted, by permission, from Méndez-Bauer, C., et al: Effects of atropine on the heart rate of the human fetus during labor. *Amer J Obstet Gynec 85: 1033–1055, 1963* (The C. V. Mosby Co., publishers).

being carried to the uterus and the fetus because of the shape of the oxygen dissociation curve. Why do you think this rather small increase in the oxygen content of the blood produces this very dramatic change?

Caldeyro-Barcia. This is very interesting. First of all, not all mothers have 100 percent oxygen saturation of arterial blood when breathing air. Analgesia or anesthesia, widely employed in obstetrics (and in experiments with pregnant monkeys), depresses the respiratory center; the supine position may further reduce pulmonary ventilation. Under these circumstances, administration of 100 percent oxygen will increase saturation and oxygen content of arterial blood. But even if the saturation of arterial blood were normal when the mother is breathing air, administration of 100 percent oxygen will cause a marked rise of maternal arterial pO_2 and a small rise in oxygen content.

In all the cases in which we have recorded pO_2 in fetal tissues, the administration of 100 percent oxygen to the mother produced a rise in fetal pO_2

similar to that illustrated in figure 47. It should be kept in mind that Type II dips appear only under abnormal conditions, which enhance the fetal hypoxia produced by uterine contractions. This fact explains the marked suppressing effect of oxygen administration on Type II dips.

LEVINE. Haven't some investigators postulated that 100 percent oxygen administered to mothers might produce placental vasospasm and cause decreased diffusion in the fetus?

CALDEYRO-BARCIA. We have never observed that administration of oxygen to the mother reduced fetal pO_2. I cannot tell you what the absolute values of fetal pO_2 are, but we know that oxygen administration to the mother caused a rise of about 5 mm Hg in peritoneal fetal pO_2 in the experiment shown in figure 47.

DAWES. If you give a pregnant ewe 100 percent O_2 to breathe, its arterial O_2 saturation rises above 100 percent (because of the increase in dissolved O_2). There is an increase in the fetal, umbilical, venous, and arterial O_2 saturation approximately commensurate with the increase in pO_2 which you observed.

JAMES. I don't think it is always possible to increase fetal oxygenation by giving oxygen to the mother. The remark of Dr. Levine, I think, has support in *in vitro* perfusion of the placenta with highly oxygenated blood. It was shown that this increased the resistance to blood flow.[13] We had some suggestive evidence of this in human beings. Following nitrogen washouts with 100 percent O_2 in five mothers undergoing elective cesarean section, babies were born clinically depressed, acidotic, and hypoxic. We suspected that unduly high oxygen tensions in the maternal blood might exert an adverse effect on the fetal circulation.

CALDEYRO-BARCIA. This was in cesarean section?

JAMES. That's right.

CALDEYRO-BARCIA. When you start opening the abdomen for a cesarean section and when you open the peritoneal cavity, the uterine tonus increases. Perhaps this interferes with maternal circulation to the intervillous space.

JAMES. I should emphasize that these babies were unexpectedly depressed. In our institution approximately 95 percent of babies delivered by elective cesarean section performed under spinal anesthesia are vigorous, scoring 7 or more.[14] In this series there were five depressed infants in a row. The only difference in technique was that the mothers had been receiving 100 percent oxygen for 1 hour. These observations suggest that prolonged administration of high concentrations of oxygen to the mother may have an adverse effect on the fetus. We still believe that high concentrations of oxygen should be given to the mother if there is a sudden episode of fetal bradycardia. However, it is important to realize that this will not always result in a normal fetal heart rate.

CALDEYRO-BARCIA. We do not have a very wide experience. We have worked with only a few subjects, because of the complexity of the recording technique. The administration of 100 percent oxygen to the mother reduced the amplitude of Type II dips in about 90 percent of the cases.

James. I think this is very reasonable if you have maternal hypoventilation from anesthesia or perhaps maternal hypotension. Fetal distress, however, may be due to other causes which cannot be remedied by giving oxygen to the mother.

Comroe. What do you mean by "fetal distress"? What he was measuring here was really a very temporary sort of thing, associated with one uterine contraction.

James. He was saying that when the baby was born after a Type II dip, it was depressed. This has also been our experience. However, we have not always been able to improve the situation, that is, to prevent the Type II dips, by giving oxygen to the mother.

Levine. It may be just a matter of degree, depending upon the severity of the depression. You have not eliminated the Type II dip in some cases but just reduced it. It may still be beyond the state of reversibility.

Segal. Would it be naive to ask whether the administration of atropine to the mother could be beneficial to the fetus under these conditions of hypoxemia?

Caldeyro-Barcia. It is premature to make any statement as to whether atropine is or is not beneficial for a distressed fetus. A potential danger is that it masks one symptom of distress, the Type II dip. By reducing the falls in the FHR (Type II dips), atropine might have the beneficial effect of increasing the fetal cardiac output and, in that way, increase the blood flow to important organs of the fetus, such as the brain. We were interested in atropine as a tool to study the mechanism of FHR changes rather than as a therapy for fetal distress.

Dawes. Do you know the effect of atropine, under these conditions, on the blood pressure of the fetal monkey?

Caldeyro-Barcia. No, I do not.

Dawes. In fetal hypoxemia the heart rate is increased; on administration of atropine, it is possible that cardiac output might fall.

Klaus. There may be a disadvantage in giving atropine if the fetus has any of the reflex responses observed in diving mammals during asphyxia. P. F. Scholander [15] has suggested that the newborn infant survives asphyxia by differential perfusion in a manner similar to the diving mammal. With asphyxia there is marked arterial vasoconstriction in the muscle beds which stops arterial inflow into the muscle. The heart rate and cardiac output markedly decrease during this period. The available oxygen is rationed to vital organs: only the brain and heart are perfused with blood. This response in the diving mammal is blocked by giving atropine.[15, 16]

Dawes. There is a danger in drawing conclusions as to what may be beneficial. During fetal asphyxia there is a centralization of the circulation, such as that described in hemorrhage in adult animals many years ago. Whether this is a good thing, remains to be considered.

When a fetus is partly asphyxiated there is vasoconstriction in some tissues and a rise of arterial pressure. We do not know what happens to cardiac output or cardiac work. In the lung, in particular, there is intense vasoconstriction, and we should therefore be most careful before concluding that the responses observed are those best fitted for indefinite survival. I think that we should observe and describe these phenomena but leave open, for the moment, the question of whether they are beneficial.

VILLEE. I would like to make the point that what tissues need is not oxygen but energy. There are various ways of obtaining biologically useful energy without oxygen. These are limited in scope, but it can occur, and tissues are known to differ in their abilities to obtain biologically useful energy without oxygen. This is largely a matter of the amount of glycogen stored. Heart muscle has a considerable store of glycogen and can function without oxygen for prolonged periods. In contrast, nervous tissues have very limited stores of glycogen and tend to suffer from oxygen deprivation before other tissues do.

AVERY. Dr. Caldeyro, do Type I dips occur only when the membranes are ruptured?

CALDEYRO-BARCIA. Yes, in a normal fetus. After rupture of the membranes, the head is subjected to much greater pressure than the rest of the fetus during uterine contractions. Now, in the case of the anencephalic (fig. 45), the stump is much more exposed to compression than in normal conditions. Type I dips are recorded even with the membranes intact. You can produce a Type I dip in an anencephalic fetus simply by compressing the stump with your finger.

COMROE. What happens to the vagus center?

CALDEYRO-BARCIA. I don't know.

FREMONT-SMITH. Isn't there, possibly, some cortical inhibition or higher-level inhibition even in the fetus, and this is absent? If it is present at all in the normal fetus, is it absent in the anencephalic?

CALDEYRO-BARCIA. I don't know.

OLIVER. Do you have any observations which would indicate that the premature infant responds differently than the full-term infant?

CALDEYRO-BARCIA. We have no experience in labor with premature infants.

JAMES. The fetal heart rate of the premature infant tends to be higher, running about 160 or 170. In our experience, in full-term infants, we had four instances out of 120 where the fetal heart rate in the mature infant was 160 or more between contractions. In all of these, the baby was in poor condition at birth. The arterial pH was below 7 and there was evidence of dysmaturity. We have therefore taken a rate of 160 or more between contractions in mature fetuses as being evidence of fetal distress. This rate may be relatively fixed with contractions.

Our recording technique was less sophisticated than Dr. Caldeyro-Barcia's; uterine contractions were monitored by clinical observation, marking the record at the beginning and end.

Figure 50 is a fetal heart rate plot from a patient with a fever who finally came to cesarean section and in whom the fetal heart rate was about 160. When fully dilated, there was an attempt at forceps delivery which was not successful. Finally, elective cesarean section was performed, and the baby was born very depressed and apneic with an Apgar score of 2, pH of 6.95, and heart rate of 158 beats per minute (recorded by ECG). The infant was intubated and the lungs expanded by positive pressure. Heart rate immediately rose to 200 beats per minute. The rate was high and rapid and did not change with manipulation by forceps.

Figure 51 is another example of a heart rate over 160 between uterine contractions, showing Type II dips as well. This was a premature infant with a prolapsed cord. The infant died *in utero*.

Villee. Dr. Caldeyro, would you call that a Type II dip?

Caldeyro-Barcia. I can't tell if I don't have the simultaneous record of uterine contractions.

Villee. There certainly is a much bigger drop.

Caldeyro-Barcia. Type I dips can be very big, too.

Villee. This went down to 60 beats per minute.

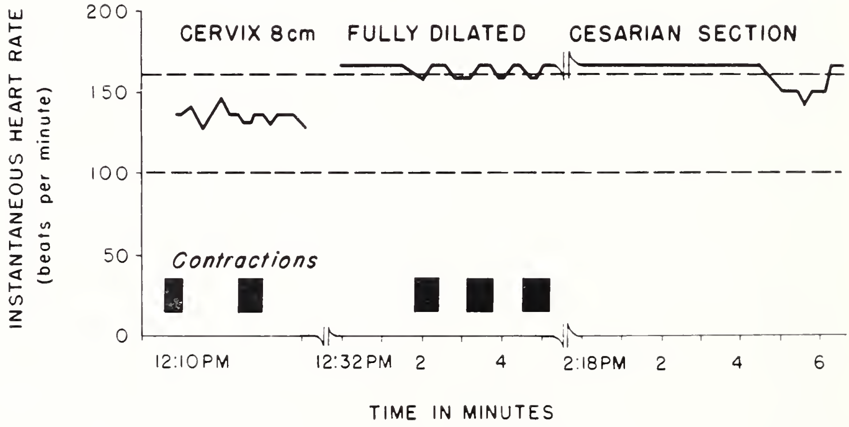

Figure 50.—Persistent fetal tachycardia associated with maternal fever, amnionitis, and dysmaturity. Heart rate remained rapid through uterine contractions, pelvic manipulations, cesarean section, and after delivery when the infant was depressed and apneic. Reprinted, by permission, from Brady, J. P., and James, L. S., with the technical assistance of Baker, M. A.: Heart rate changes in the fetus and newborn infant during labor, delivery, and the immediate neonatal period. *Amer J Obstet Gynec 84: 1–12 (July 1) 1962* (The C. V. Mosby Co., publishers).

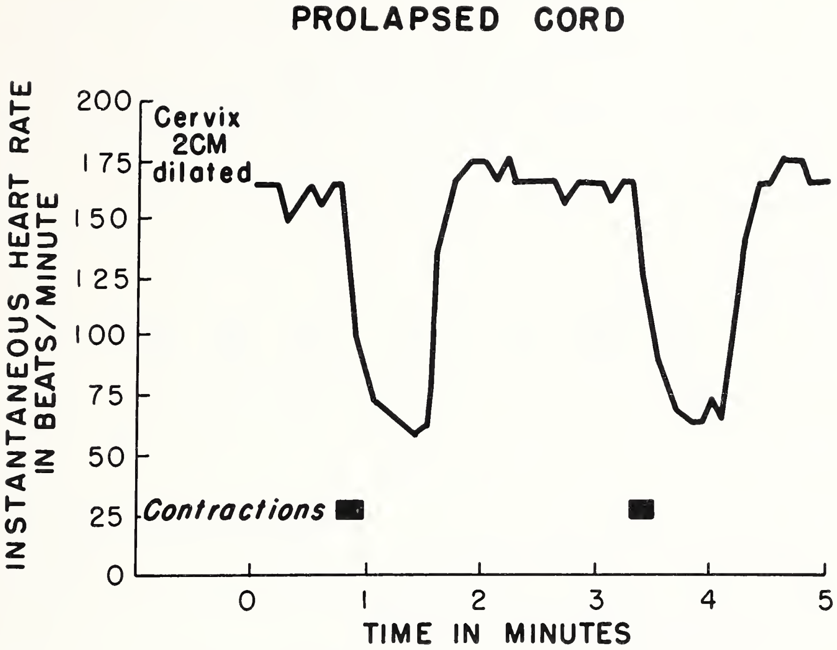

Figure 51.—Record of previable fetus with prolapsed cord. Contractions were being induced with oxytocin and were of very short duration (10 seconds) but caused a profound fall in heart rate from 167 ±10 to 60. Death *in utero* occurred some hours after this record was taken. Reprinted, by permission, from Brady, J. P., and James, L. S., with the technical assistance of Baker, M. A.: Heart rate changes in the fetus and newborn infant during labor, delivery, and the immediate neonatal period. *Amer J Obstet Gynec 84: 1–12* (*July 1*) *1962* (The C. V. Mosby Co., publishers).

Caldeyro-Barcia. How long did the FHR remain at that low level, Dr. James?

James. These rates were down to below 100 beats per minute and remained low for over 50 seconds after the time when the contractions had ceased. Figure 52 is another example of fetal tachycardia with bradycardia during contractions. This pattern was seen for nearly 2 hours and probably was not the result of fetal hypoxia, because the bradycardia was sudden and brief. It may have been due to carotid sinus pressure during contractions, since the infant was a face presentation. The infant scored 2 at 1 minue and required resuscitation.

Caldeyro-Barcia. Are these the original records?

James. No, they have been plotted every 4 seconds. Figure 53 is an example of bradycardia, which was not changed by giving oxygen to the mother. This was a rate which went down with contractions and remained

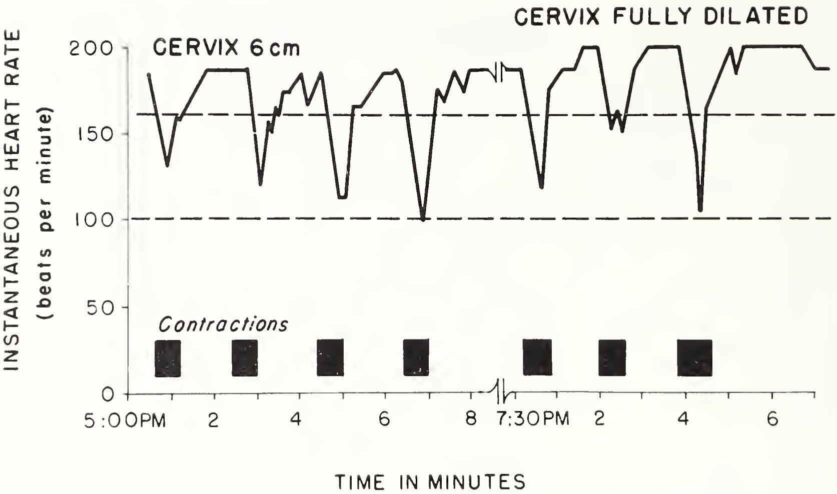

Figure 52.—Face presentation. Baseline tachycardia with relative bradycardia during contractions. No evidence of any cord complication at delivery. Reprinted, by permission, from Brady, J. P., and James, L. S., with the technical assistance of Baker, M. A.: Fetal electrocardiographic studies: Tachycardia as a sign of fetal distress. *Amer J Obstet Gynec 86: 785–790 (July 15) 1963* (The C. V. Mosby Co., publishers).

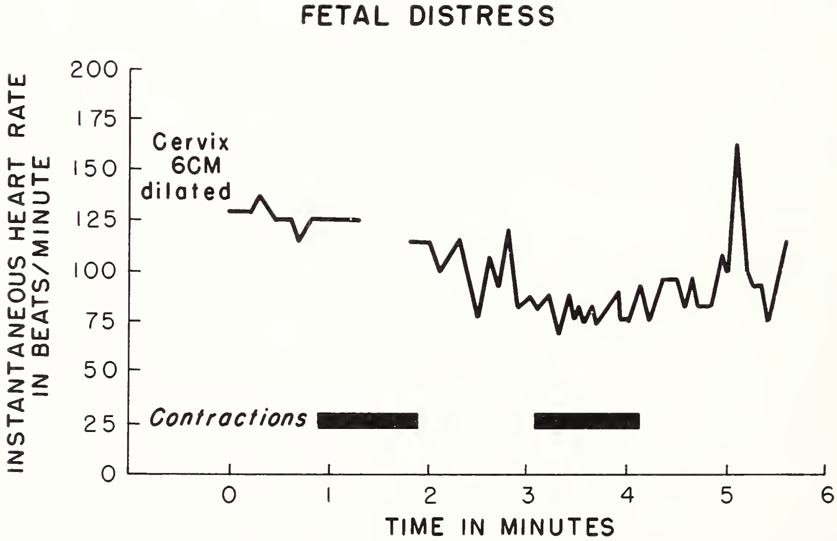

Figure 53.—Fetal heart rate under 100 throughout the second contraction and for 1 minute afterward. Clinical bradycardia noted. An emergency cesarean section produced a depressed infant, score 1. Reprinted, by permission, from Brady, J. P., and James, L. S., with the technical assistance of Baker, M. A.: Fetal electrocardiographic studies: Tachycardia as a sign of fetal distress. *Amer J Obstet Gynec 86: 785–790 (July 15) 1963* (The C. V. Mosby Co., publishers).

down in the region of 75. There was no change when the mother was receiving 100 percent oxygen.

AVERY. I am particularly interested that the fetal heart rate oscillates, because the heart rate of the newborn infant on occasion also oscillates. I would like to illustrate ECG complexes, one right beneath the other, recorded from a premature infant (fig. 54). The ECG complex is triggered by the R wave, and the broad white band down the middle is the second R wave. The top part was recorded during a diaper change. The heart rate is speeded up because the R–R interval is shorter. Then the rate oscillates over the next period until it reaches its resting value, which is about 20 beats per minute slower.

SCHAFER. Do you see the same type of fluctuation if you make your recording over longer periods of time?

AVERY. Yes. We have done them continuously over 36 hours, and these things occur only after there has been an induced change in rate. The heart rate may be perfectly steady for 4 and 6 hours. If the infant is stirred, he may go through this.

CROSS. The same thing has been recorded in recovery from exercise in the adult, and I believe it is not understood there either.

SILVERMAN. We have made some observations of cardio-inhibitory reflexes in premature infants during the neonatal period. A surprisingly high proportion—well over half—of these infants exhibit profound bradycardia in response to pressure on the anterior fontanelle, eyeball, or carotid bodies.

JAMES. There is one point I wish you would comment on, and that is the difficulty of blocking this response with quite large doses of atropine.

SILVERMAN. We made some unsuccessful attempts to block these responses, but the observations were not systematic enough to warrant a statement.

DAWES. Why should you expect to block it with atropine? Surely, the heart rate is controlled not only by the vagal efferent fibers but also by the sympathetic fibers. Even if you have blocked the vagal efferents, you still have the sympathetic efferent nerves to the heart.

COMROE. The changes are smaller, though.

DAWES. The changes are certainly smaller, but this may well explain the persistence of some of the alterations in Dr. Caldeyro-Barcia's experiments, even after the administration of atropine, although one must remember that hypoxemia can cause bradycardia in a denervated heart. Do you think the bradycardia shown by Dr. Caldeyro-Barcia could be due to stimulation of the systemic arterial chemoreceptors?

COMROE. This is a possibility. Stimulation of the carotid body in the dog produces bradycardia as its primary response, particularly if there is no associated hyperpnea. More work is necessary in order to be sure of the origin of the bradycardia; it could come from three or four different places.

SEGAL. If we return to the Type II dip and ignore the neonatal considerations for a moment, I observed on one of Dr. Caldeyro's slides that oxytocin

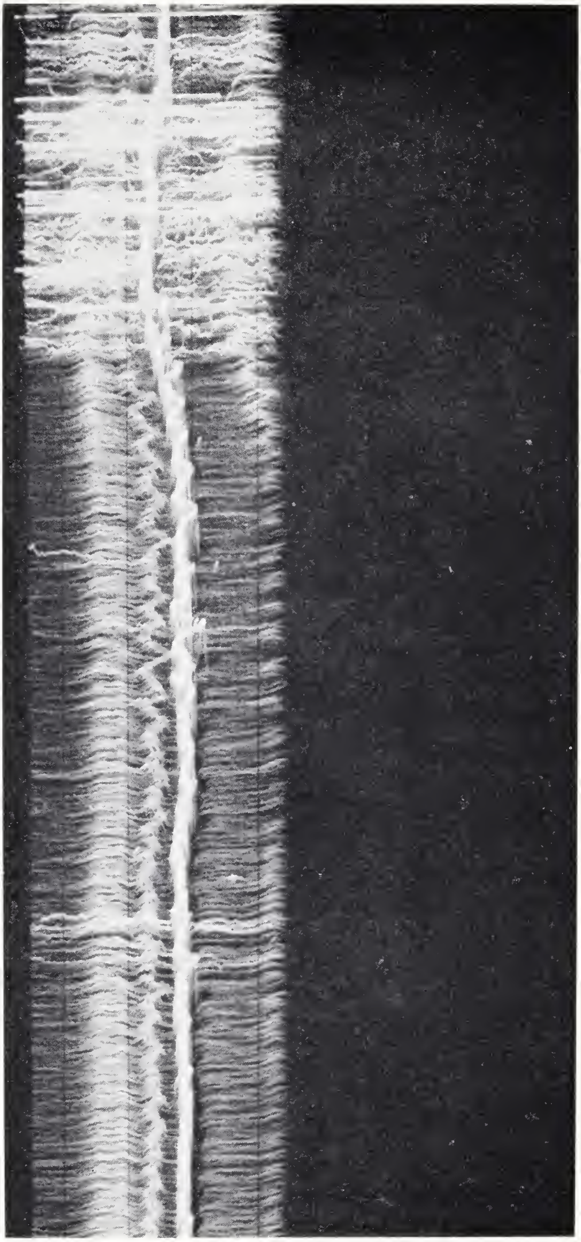

Figure 54.—ECG complexes "packed" one beneath the other so that 12 minutes of continuous ECG is displayed in this single contourograph. Rate is faster in upper portion of figure, during activity of infant. There are oscillations in rate before the resting rate is resumed, at bottom of photograph. (Reproduced by courtesy of Mr. George Webb, Department of Biomedical Engineering, Johns Hopkins Medical School.)

had been used during labor, and also saw the word "pitocin" on one of Dr. James' slides. Is there any important relationship between administration of an oxytocic and the occurrence of Type II dips?

CALDEYRO-BARCIA. Oxytocin increases the frequency and the intensity of uterine contractions. Excessive dosage of oxytocin will induce abnormally strong contractions (amniotic pressure rising above 60 mm Hg), or abnormally frequent contractions (the interval between peaks shorter than 120 seconds). Excessive uterine contractility is one factor that contributes toward the production of Type II dips, but this may be facilitated by other factors. Every agent that reduces the exchanges between mother and fetus facilitates the production of Type II dips by contractions. Reduced pulmonary ventilation of the mother, maternal arterial hypotension, loop of the cord around the fetal neck are but a few examples.

COMROE. What produces the uterine contraction?

CALDEYRO-BARCIA. The uterus is automatic and has its own pacemakers. It has areas (pacemakers) where the cells spontaneously show the prepotential and then discharge. This stimulation spreads to a more or less large number of fibers, depending on their excitability and conductivity.

COMROE. I merely wanted to know whether there was any hormone liberated into the bloodstream that was required for the contraction, and whether this could affect the placental circulation as well as the uterine muscle.

CALDEYRO-BARCIA. The pregnant human uterus, disconnected by spinal anesthesia from the central nervous system, apparently produces the same type of contractions as in normal conditions. There are many factors which seem to be involved. Oxytocin, in concentrations of a few microunits per milliliter of blood, produces very strong uterine contractions. Whether oxytocin is an indispensable factor for labor, or is just a coadjuvant factor, is still the subject of research.

COMROE. What releases it?

CALDEYRO-BARCIA. This is not yet known. In the second stage of labor, apparently the distention of the birth canal reflexly causes release of oxytocin. This seems to be more or less established. What is not known is whether there is some oxytocin released at the initiation of labor or during prelabor, or whether there is none.

SEGAL. Has there been any experimental isolation of the uterus from the central nervous system, or have all the observations on such effects been made purely in instances of clinically diagnosed transection of the cord?

CALDEYRO-BARCIA. At least the spinal cord has been blocked by local anesthetics, such as procaine and others. Cases of transection of the spinal cord have been reported in which labor has occurred more or less normally, at least from the uterine point of view.

RAMSEY. There are isolated muscle strip studies which also indicate the automatic nature.

Schafer. Do you see changes in the fetal heart rate with the mild uterine contractions which occur throughout most of pregnancy?

Caldeyro-Barcia. They have no effect. The amniotic pressure must rise to approximately 30 mm Hg before one sees any effect in the fetus.

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*Published since conference was held.

Histochemistry in Embryonic Lungs

ASPECTS OF PULMONARY DEVELOPMENT

SOROKIN. To begin with, lungs are formed from essentially two tissues, one being connective tissue and the other epithelium derived from the floor of the pharynx. The various cells of mature lungs become distinct from those of the primordial tissues at different times but in a predictable sequence; they conform to an ontogenetic pattern present during the development of many mammalian lungs. Both morphological and chemical changes contribute to a description of this pattern. In chemical changes, those of enzyme and substrate are both involved.[1]

Morphological changes in developing lungs are more widely known than chemical changes. Fluctuations of glycogen storage in fetal lungs may be considered as an example of the latter. This carbohydrate is abundant in fetal lungs. In the epithelium it is first deposited in cells of the tracheal bud. Subsequently, as the bronchial tree expands, glycogen becomes concentrated in cells of the terminal buds, where cell division is most active. As earlier-formed cells mature, their glycogen stores decline. Glycogen is also present in the connective tissues of developing lungs; those in the younger population of premature infants contain much glycogen.[2] While fluctuations of epithelial glycogen apparently mirror underlying developmental processes, those of the mesenchyme reflect a secondary function of lungs in carbohydrate storage. Claude Bernard [3] found abundant glycogen in the lungs as well as in the livers and muscles of animals in hibernation or in a state of torpor due to cold. The reserves diminished after the animals had been aroused.

It is clear that among different species pulmonary development does not necessarily proceed to an advanced state before the advent of birth; differentiative events are continuous from prenatal to postnatal periods. Thus, the lungs of the sheep are relatively well developed at birth; the lungs of the rat or mouse are relatively immature. Those of man lie in between. Among mammals the record for pulmonary immaturity at birth is probably held by the opossum,[4] whose gestation period is brief (12 days, 16 hours).

At maturity, the lungs of most mammals contain four distinct epithelial cells in the pseudostratified lining of the trachea and bronchi, two or three in the bronchioles, and two in the alveolar regions. These cells and those derived from pulmonary mesenchyme possess, in varying degree, capacity for specialized function. Some of this capacity can be deduced from study of cytochemical preparations. Three examples are given (figs. 55, 56, 57); they reveal, each by demonstrating the activity of one enzyme in the schema, the presence of different pathways of carbohydrate metabolism in the lung of the same mouse, respectively the glycolytic route, the citric acid cycle, and the hexose monophosphate shunt. Of these, glycolytic activity, represented by activity of glyceraldehyde-3-phosphate dehydrogenase,[5] is the most evenly distributed among cells of the lung (fig. 55). Activity of the citric acid cycle, represented by succinic dehydrogenase,[6] is well represented in those regions of the lung having high requirements for oxidative energy, either for synthetic or motor functions; hence, in the mouse's lung, it is not surprising to find the greatest activity of this enzyme in the adventitial cardiac muscle of the pulmonary veins, followed, in order, by activity in the epithelium lining the airways, the smooth muscle, and the alveolar walls. In contrast to the preceding, activity of the hexose monophosphate oxidative pathway, represented by glucose-6-phosphate dehydrogenase,[7] seems to be associated with those regions of the lung that elaborate secretory products. It is conspicuous for its absence from the muscular tissues, both plain and cardiac (fig. 57).

ACTIVITIES OF THE GREAT ALVEOLAR CELL*

Within alveolar walls, a number of cells, roughly cuboidal in shape, possess activity for glucose-6-phosphate dehydrogenase (fig. 60). These are the great alveolar epithelial cells (*"les grandes cellules alvéolaires"* of

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*See footnote page 82.

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Figure 55.—Preparation of a mouse's lung demonstrating localization of activity of glyceraldehyde-3-phosphate dehydrogenase. Epithelium, muscle, and alveolar stroma are all active. Nitro-blue tetrazolium, pH 7.2, 10 minutes at 37° C. X 80.

Figure 56.—Same lung as figure 55, demonstrating succinic dehydrogenase. Activity is strongest in cardiac muscle of the vein, followed by that in bronchial epithelium and smooth muscle. Nitro-blue tetrazolium, pH 7.6, 20 minutes at 37° C. X 80.

Figure 57.—Same lung as figures 55 and 56, demonstrating glucose-6-phosphate dehydrogenase. Bronchial epithelium and great alveolar cells are especially reactive; muscular tissues are not. Nitro-blue tetrazolium, pH 7.3, 20 minutes at 37° C. X 80.

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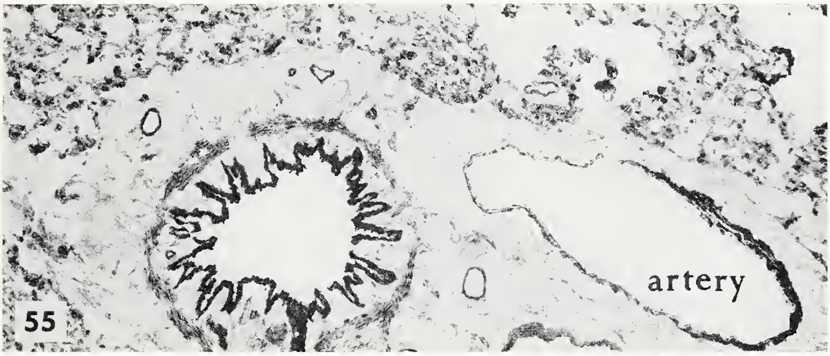
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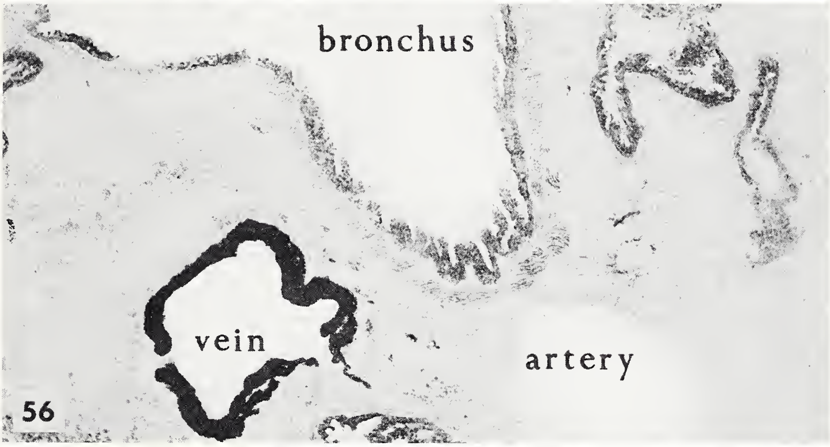
artery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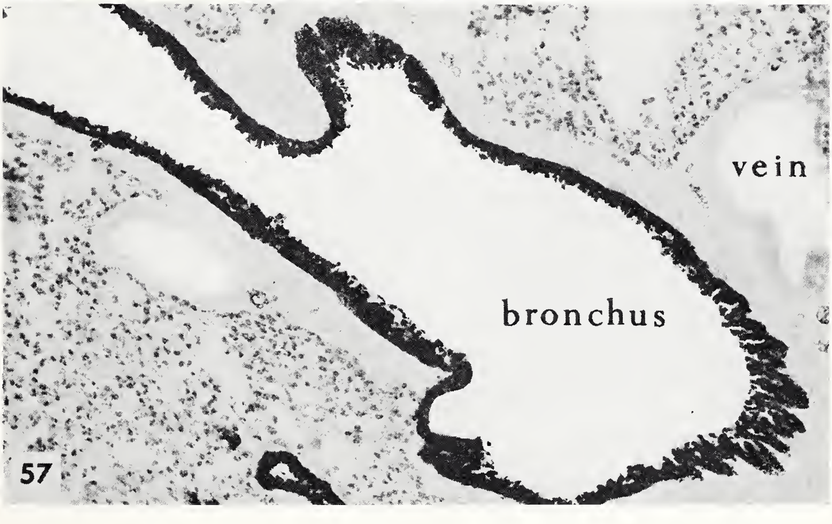
bronchus
vein
artery


57
vein
bronchus

Policard et al [8]) (figs. 58, 59) as distinguished from the squamous, or small alveolar epithelial cells, which form the thin but continuous lining of the alveolar spaces. Combining the cytochemical evidence presented with information from the biochemical literature,[9, 10] one may conclude that in these great alveolar cells, as well as in the epithelium of bronchi and bronchioles, the hexose monophosphate oxidative pathway operates at a functionally significant level.[11] It is not clear, however, just what percentage of the total energy available to the cells is furnished by this route. Nonetheless, through dehydrogenation of glucose-6-phosphate, reduced triphosphopyridine nucleotide becomes available for various synthetic processes. Evidence that such use is made of the reduced coenzyme comes from other tissues. High activities of glucose-6-phosphate and 6-phosphogluconate dehydrogenases were recorded by Glock and McLean [9] in adrenal glands and lymphatic tissues in general, but the highest values of all were found in lactating mammary glands of rats, where a sixtyfold increase in the activity of glucose-6-phosphate dehydrogenase was measured in the period between the end of pregnancy to the end of lactation. In this interval the weight of the mammary glands remains nearly constant, when corrected for milk content; the authors linked the changes in enzymic activity with synthesis and secretion of the lipid-rich (20% fat) milk. Enzymic activity of skeletal muscle was at the opposite extreme.

The great alveolar cells often pass unnoticed in routine paraffin sections of lungs. Careful observers, nevertheless, have long been able to recognize them in such preparations, because of their large, vesicular nuclei and foamy cytoplasm. (A number of other names have been given these cells, "septal cells" being the most popular. Unfortunately, the same term has

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*This investigation was supported by a Public Health Service Research Career Development Award and Research Grant GM–10949–01 from the Division of General Medical Sciences, National Institutes of Health.

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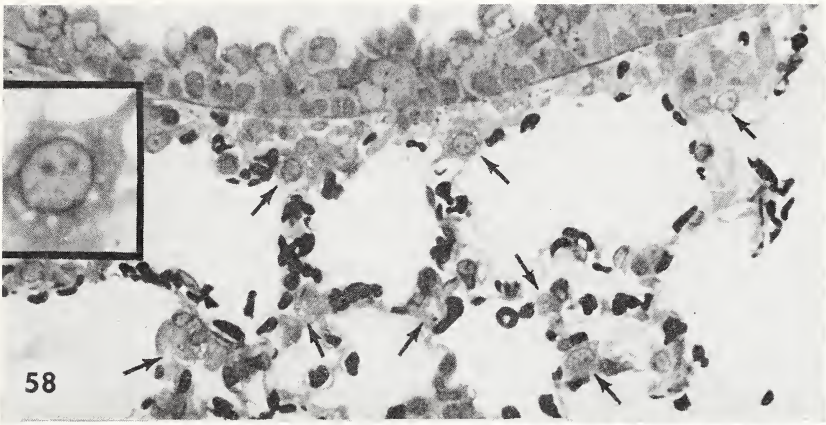
FIGURE 58.—Alveoli near a bronchiole in a rat's lung. The bronchiolar epithelium crosses the top of the field. Capillaries of the alveolar walls frequently appear in cross section; in them, erythrocytes (*black*) are recognizable. Great alveolar cells (*arrows, inset*) are characteristic in shape and location. Osmium tetroxide fixation, embedded in Epon. Richardson's stain. X 300. Inset, X 1,750. Reprinted, by permission, from Greep, R. O.: *Histology,* ed 2. New York, McGraw-Hill Book Co., 1966.

FIGURE 59.—Tracing of figure 58. Bronchiolar epithelium (*above*) and great alveolar cells (*scattered below*) are blackened. Compare with figure 60. X 300.

FIGURE 60.—Frozen section of a mouse's lung demonstrating glucose-6-phosphate dehydrogenase. Great alveolar cells (*arrows*) and bronchial epithelium are reactive; compare with figures 58 and 59. The localization of the reaction is similar in the rat's lung. X 300.



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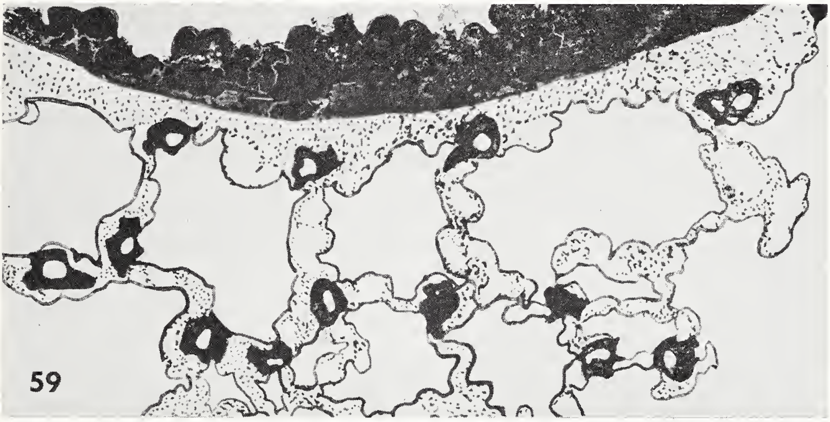

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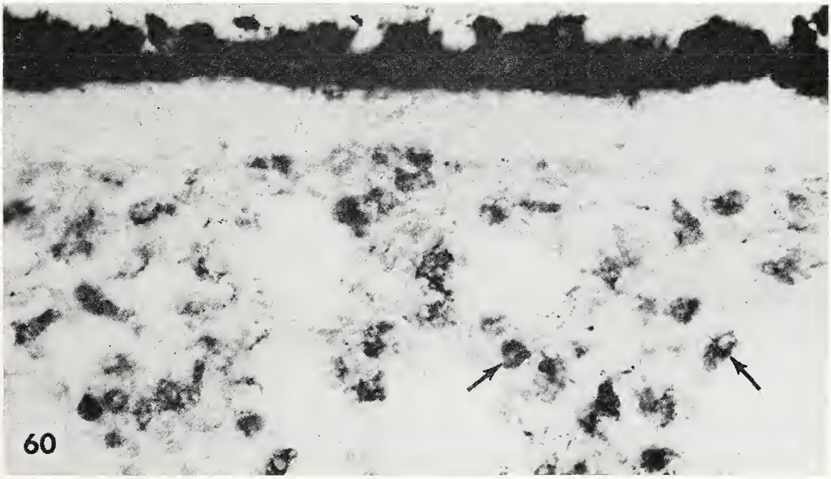

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been applied to other intraalveolar elements; hence, it has lost its meaning.) As seen in thin sections of lungs embedded in plastic, such cells are readily identified in alveolar walls by their shape, large nucleus with nucleolus and dense cytoplasm containing a number of conspicuous ovoid bodies.

Electron micrographs of great alveolar cells provide additional details (figs. 61, 62). Part of the cell surface opens on the alveolar space; part is overlapped by squamous processes from small alveolar cells. At such points, the two cell types are linked by terminal bars. In addition, the presence of microvilli along the free surfaces of great alveolar cells qualify them as epithelial cells (fig. 62).

Clements. Do you attach any particular significance to the microvilli?

Sorokin. Microvilli provide cells with increased surface exposure, in this case to the alveolar space; but their presence can be noted in both secretory and absorptive cells. In contrast to squamous alveolar epithelial cells, great alveolar cells have few pinocytotic vesicles along their free surfaces.

The cytoplasmic matrix of great alveolar cells has greater electron density than the cytoplasm of neighboring cells (fig. 61). Within, lie extensive, although not highly ordered, lamellae of the granular endoplasmic reticulum, free ribosomes, several regions containing membranes of the Golgi apparatus, numerous round to rod-shaped mitochondria, multivesicular bodies,[12] and a number of membrane-bound ovoid bodies approximately the size of mitochondria but greatly exceeding their range of diameters (fig. 63); these are the cytosomes.

Comroe. I am told that this particular structure is not seen in this form in any other tissue in the body. Is that really correct?

Sorokin. No, it is not correct. In our department, Dr. Daniel S. Friend[13] examined kidney biopsy specimens from a patient with Fabry's disease. In this disease the relevant clinical finding is phospholipiduria. Dr. Friend found multilamellar bodies similar to the pulmonary cytosomes in visceral epithelial cells of Bowman's capsule.

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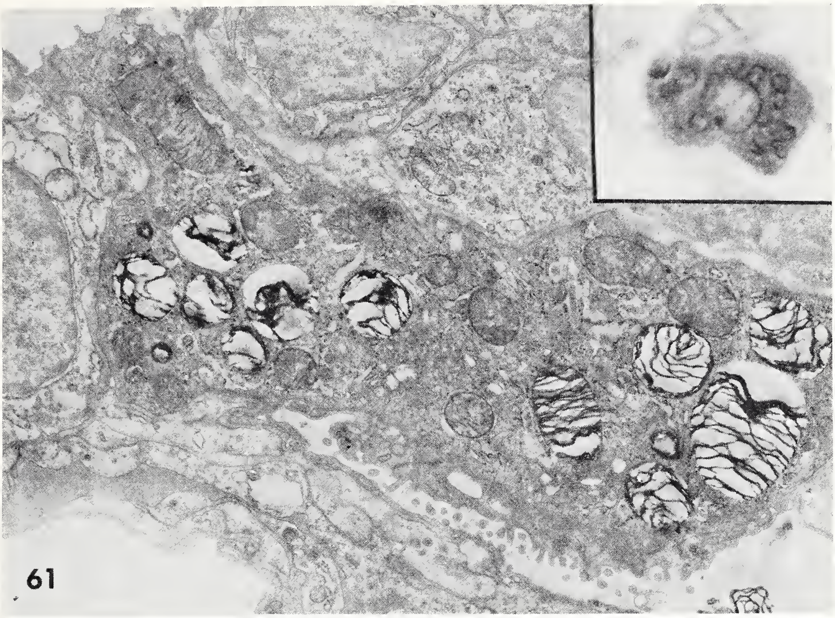
Figure 61.—Low-power electron micrograph, showing a great alveolar cell in position in the rat's lung. Part of the cell is exposed to the alveolar space, part rests on a basement lamina, and part contacts the attenuated protoplasmic sheets of squamous alveolar cells. Within, the disposition of organelles and inclusions can be seen. *Inset,* light micrograph of a similar cell. Glutaraldehyde-osmium tetroxide fixation, embedded in Epon. Karnovsky's lead stain. X 8,200. *Inset,* stained with toluidine blue. X 1,600.

Figure 62.—Organelles and inclusions in the cytoplasm of a great alveolar cell. The free surface of the cell is provided with short microvilli (mv) but exhibits no evidence of pinocytosis. The cell joins another containing a multivesicular body (mvb) at the upper left; the point of junction is sealed by a terminal bar. Osmiophilic material occupies cisternae of the ergastoplasm (er). Mitochondria appear intact. Prepared in the manner of figure 61. X 26,000.



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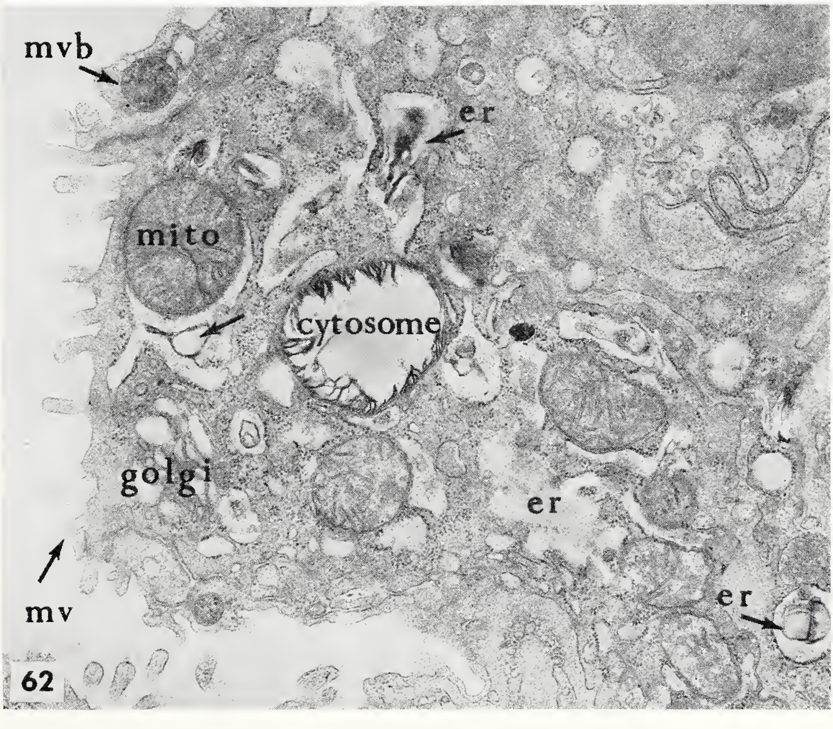

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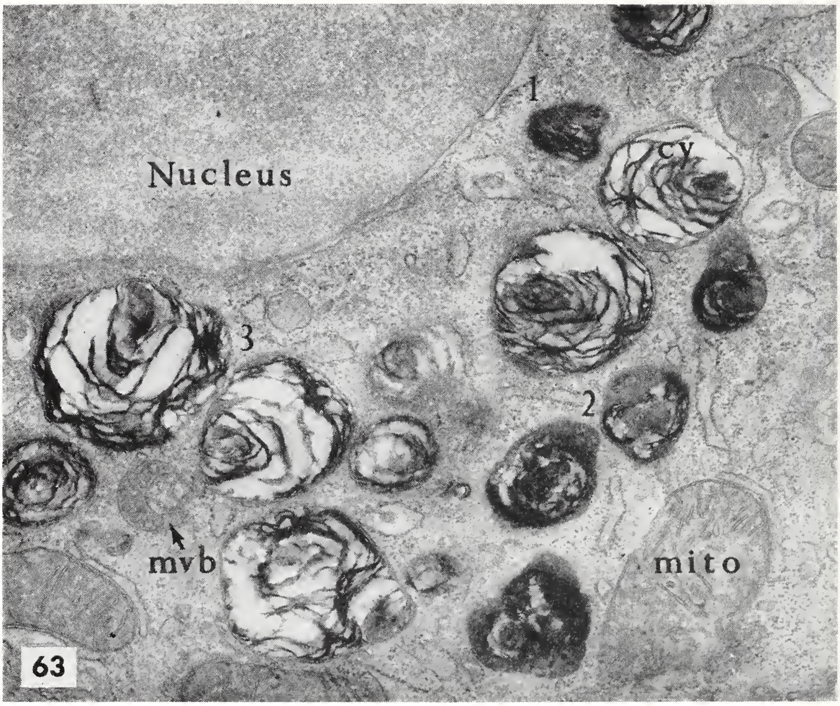


FIGURE 63.—Cytosomes (cy) in the cytoplasm of a great alveolar cell in a rat. They exhibit a range of sizes (1, 2, 3). The smaller ones bear no resemblance to mitochondria (mito). The larger ones appear extracted. A multivesicular body (mvb) is conspicuous. Glutaraldehyde-osmium tetroxide fixation, embedded in Epon. Karnovsky's lead stain. X 28,000.

In frozen sections of lung prepared for light microscopy, sudanophilic droplets, for the most part acetone fast, can be seen in certain alveolar cells, probably great alveolar cells. In the same slides, however, sudanophilia is far more conspicuous in granulocytes found within the capillaries. The cytosomes are periodic acid-Schiff positive; in this reaction, use of plastic sections assures accurate identification. Lungs fixed in osmium tetroxide and prepared for electron microscopy contain cytosomes that appear partly osmiophilic and partly extracted; the portion remaining has an affinity for heavy-metal stains (figs. 61, 62, 63). The fixative action of osmium apparently depends upon its binding to lipids at points of unsaturation in the carbon chains.[14, 15]

Using permanganate fixation, the cytosomes are denser and more finely lamellated than after osmium fixation.[16] This suggests that cytosomes contain part lipid, of which most is phospholipid.

Within the cisternae of the granular endoplasmic reticulum of great alveolar cells one frequently encounters strands of osmiophilic material that share with cytosomes such properties as a partially extracted appearance and an affinity for heavy-metal stains (fig. 62). Neighboring cells of other types do not contain such material; hence, the observation provides some evidence that cytosomal material is first synthesized within the ergastoplasm. Numerous morphological studies on the elaboration of secretory products by cells point to the granular endoplasmic reticulum as the site of synthesis of proteinaceous secretory products.[17, 18] Secretory products are then usually transferred to the Golgi region of cells, where they are set out in the cytoplasm as discrete membrane-bound secretory droplets, which ultimately are released from the cell by fusion of the surface cell membrane with those of the droplets.[19]

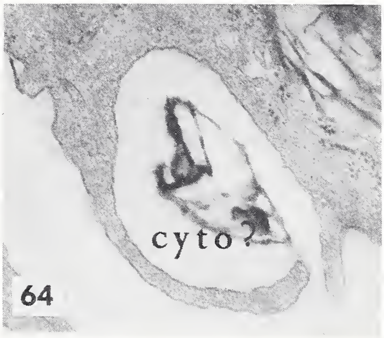
VILLEE. Are you saying that you are not quite sure whether these cytosomes are derived from mitochondria?

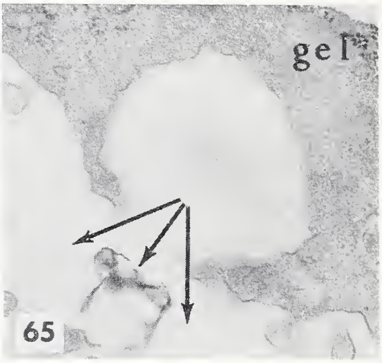
SOROKIN. I think there is little evidence to support the concept of cytosomes being derived from mitochondria. Rather, the lipid-rich material contained within these membrane-bound bodies seems to be made in the cell's synthetic centers and stored as cytosomes. When not excessively extracted, the contents of large cytosomes have the form of myelin figures. At present, the identity of material within ergastoplasmic cisternae and cytosomes remains unproved. Similarly, that there is any involvement of the Golgi apparatus or multivesicular bodies in the synthetic process, awaits demonstration.

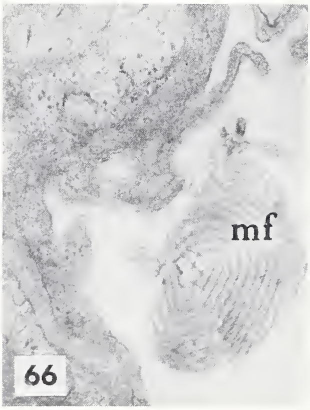
Indirect evidence suggests that cytosomes are secreted and not absorbed by great alveolar cells, for, when challenged by particulate material known to stimulate phagocytosis, the alveolar lining responds feebly or not at all.[20, 21] Alveolar phagocytes, in contrast, are markedly stimulated.[20] Moreover, they contain relatively few cytosomes. If cytosomes were bodies absorbed from alveolar spaces, one would expect to find most of them in phagocytes. Electron micrographs provide some direct evidence, furthermore, that cytosomes are secreted by the epithelial cells (figs. 64, 65). Myelin figures, in addition, are occasionally encountered in alveolar spaces (fig. 66).

The presence of comparatively few cytosomes in alveolar phagocytes strengthens the long-held argument that the phagocytes are derived from great alveolar cells; in rabbits, biochemical and cytochemical evidence distinguishes the wandering cells from polymorphonuclear and mononuclear phagocytes.[22, 23] In possessing cytosomes, moreover, both of these alveolar cells share a property with the epithelium of primitive lungs. In the salamander, for example, Dr. Elizabeth Hay and I [24] found lamellar bodies like cystosomes in both ciliated and nonciliated cells (figs. 67, 68, 69).

KLAUS. Aren't these bodies much larger in the salamander? Don't they appear to be different even though osmic acid is used? [25]







Figures 64 and 65.—Surface portions of two great alveolar epithelial cells are arranged in a manner to suggest secretion of cytosomes (cyto) into the alveolar space. Surrounding the "secretory packet" the cytoplasm is unusually fibrous, as if locally gelled. Lung of a rat. Glutaraldehyde-osmium tetroxide fixation. X 40,000.

Figure 66.—A myelin figure in the alveolus of the lung from an adult rat. Glutaraldehyde-osmium tetroxide fixation. X 27,000.

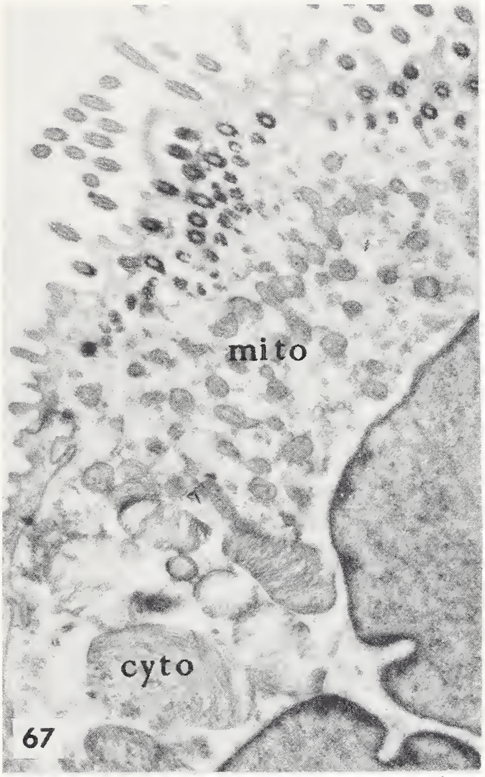
⟶

Multilamellar bodies similar to cytosomes are pictured in the columnar epithelial lining of the lungs of *Amblystoma punctatum* during metamorphosis. Osmium tetroxide fixation, embedded in prepolymerized butyl methacrylate. Stained with lead.

Figure 67.—Multilamellar bodies (cyto) in a ciliated cell. The mitochondria (mito) are considerably smaller than the largest phospholipid bodies of these cells. X 8,900.

Figure 68.—An abundance of such structures is present in nonciliated cells. X 4,500.

Figure 69.—Cytosome-like structures (cyto) in mucoid-secreting cells. X 5,200.



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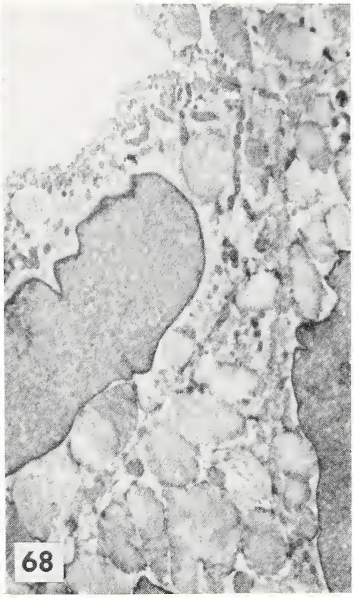

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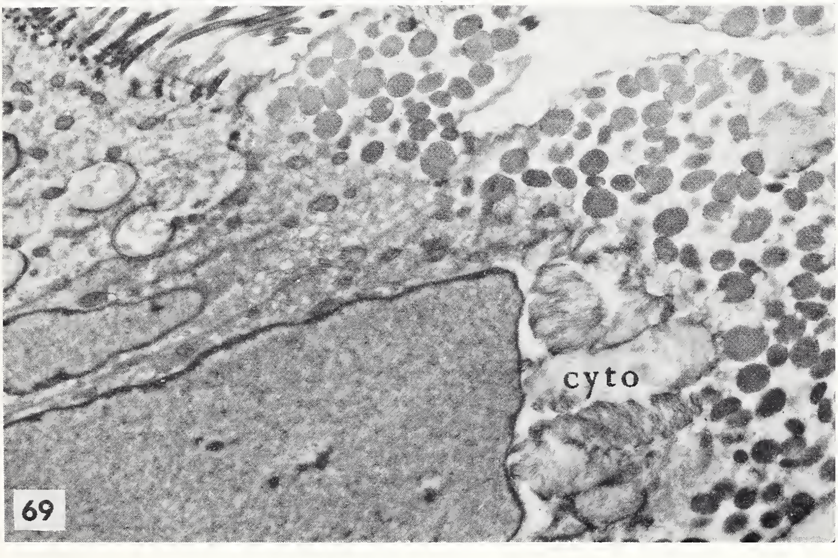

69

SOROKIN. When you are dealing with myelin figures, such as these in cells, you will find them, I think, to have a great variety of shapes. Revel, Ito, and Fawcett [26] made electron micrographs of phospholipid preparations from eggs. The myelin figures they obtained were of greatly varied configuration.

Cytosomes begin to appear midway in the development of lungs, judging from preliminary reports in mice [27] and in man.[28] In rats, a few are apparent in cuboidal epithelial cells of prealveolar regions at 21 days of gestation (fig. 70) and in salamanders at metamorphosis. In mice, Avery [27] correlates the appearance of cytosomes with onset of surface activity in the lungs; in rats, the bodies appear at a time when glycogen is declining and glucose-6-phosphate dehydrogenase is becoming active in the pulmonary epithelium.

In this discussion, attention has been focused on evidence for secretory capacity and function by the great alveolar epithelial cells of mammalian lungs. In broad outline, there is good reason to consider them active in secretion of a phospholipid-containing product, possibly identical with the "surfactant" that functions in stabilizing alveolar surface tensions. The cell product is stored within membrane-bound bodies, termed "cytosomes" for convenience. These bodies lie in the cytoplasm of great alveolar cells and to a limited extent in the cytoplasm of alveolar phagocytes. Cytosomes are easily studied in light microscopy if use is made of the periodic acid-Schiff reaction on sections embedded in plastic. In electron microscopy they are recognizable by their resemblance to myelin figures. In developing lungs they first appear in cuboidal epithelial cells near the time of alveolar formation.

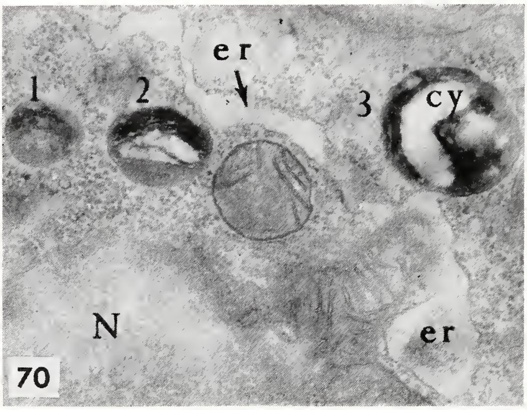

FIGURE 70.—Detail of a cuboidal epithelial cell in the lung of a 21-day fetal rat. Nucleus (N) and endoplasmic reticulum (er) are recognizable, as are a few bodies (1, 2, 3) identifiable as cytosomes (cy). They do not resemble the mitochondria located nearby. X 18,500.

Comroe. Would you repeat what you said about the muscle and the pulmonary vein?

PULMONARY VEINS

Sorokin. Cardiac muscle is found in the adventitia of the pulmonary veins of small mammals, irrespective of taxonomical order. In the shrew, bat, mouse, gerbil, and kangaroo rat the cardiac coat extends nearly to the venules.

Fremont-Smith. How about large mammals?

Sorokin. The larger the animal, the less extensive the coat. In human beings, for instance, cardiac muscle extends only a centimeter or so along the veins; it does not cross the hilum. In the guinea pig, the coat covers the large intrapulmonary veins.

Comroe. I hate to ask this with Dr. Dawes in the room, but what about the dog?

Sorokin. In the collie, I found the coat extends to the hilum. Cardiac muscle has been known to occur in some pulmonary veins since the time of Räuschel;[29] subsequently, it has been rediscovered there a number of times.[30-32]

Fremont-Smith. Has any functional activity been shown for it?

Sorokin. A number of authors have speculated that in these veins contraction of the cardiac muscle facilitates return of blood to the heart. Such assistance would benefit small animals which have rapid heart rates. From preliminary studies in anesthetized rats and guinea pigs, using an oscilloscope and small electrodes placed directly on the vessels, we concluded that a wave of contraction begins peripherally and travels along the cardiac muscle coat of the pulmonary veins toward the heart.[33]

MacLeod. What are the criteria for saying those are cardiac muscle cells?

Sorokin. The criteria are morphological ones, cross-striated muscle cells having central nuclei and intercalated disks.

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Transition From Intrauterine to Extrauterine Life

Comroe. The transition period from fetal life to newborn life can be likened to the preparation of a seven-course dinner in which the cook must see that the canapés and the soup, the salad and the steak, the vegetables, the coffee, and the dessert are all ready, either at the same time or in the proper sequence, or everything may be spoiled. So, when the fetus becomes a newborn, everything has to be done on time, either all together or in proper sequence, or things may be pretty much spoiled.

Air has to get into the lung, the pulmonary circulation suddenly must increase, the placental blood flow must decrease or be shut off, the ductus arteriosus and the foramen ovale must close, and ventilation must begin and be adjusted to meet the metabolic needs of the newborn in its new environment. This means taking care of oxygen, CO_2, nutrients, and temperature regulation, among other things. This is a big job. There is probably more crucial physiologic regulation in this short time than is ever required of man at any other time in his entire life.

Today, we should concentrate upon what we *don't* know rather than what we *do* know. We should attempt to find the answers to such important questions as (1) the first breath from the point of view of the physical and chemical factors involved; (2) the first breath from the physiologic point of view—Dr. Dawes says it is equally important to discuss not only the first breath but also the second and third, and also why the infant after it takes the first breath keeps on breathing; (3) the cardiovascular changes; (4) the metabolic needs.

Dr. Clements will get us into the surfactant story—the background, our present knowledge, and where we go from here.

PULMONARY SURFACTANT*

Clements. Dr. Sorokin has demonstrated how the fetal lung prepares for emergence from an aquatic into an atmospheric environment. He showed us the cellular preparations which are made for the development of a large potential air space in the lung and how, anticipating the onset of external respiration, the area of the blood-air barrier is very greatly multiplied. His slide, however, did not emphasize what preparations are made for the *maintenance* of a large air-to-blood contact, and it is around this question that I would like to address my remarks.

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It is almost trite to say that this large area for respiratory exchange is accomplished by subdivision of the air spaces into small, highly curved units which, by virtue of their moistness, have a tendency to collapse because of surface tension at the tissue-gas interface. As a result of this contact, there is not only a tendency to atelectasis but also the possibility of lysis of alveolar epithelial cells, if they are directly exposed to the liquid-gas interface.

There is a third problem. The balance of forces which act to distribute water or fluid within the lung is affected by the tension in the tissue-to-gas interface. Thus, the dryness or openness of the alveolar structure is also dependent upon the quality of this interface.

I believe that the property of the interface is modified by the secretion from alveolar cells of surface-active material, which is now generally called "surfactant." Its function is to reduce the interfacial tension (reducing the tendency to collapse on this account) and to place a barrier layer between the air interface and the alveolar epithelial cells (protecting cells against surface lysis) and, finally, as a consequence of both of these effects, to maintain the impermeability of the alveolar membrane against effusion and accumulation of plasma products in the air spaces.

When there is interference with the generation or maintenance of a surface-active lining of the alveoli, we should expect to see a triad of effects—effusion, alveolar cell damage, and atelectasis—and, indeed, this occurs to a certain degree and in varying proportions.

We have some knowledge about the chemical composition of surfactant. Briefly, it is a complex lipoprotein which contains many kinds of lipids but particularly phospholipids which are different from those that make up lipoproteins extractable from the blood or from other organs in that their substituent fatty acids are unusually highly saturated. This is of interest to us because in *in vitro* experiments on pure compounds we can show that strong surface activity is related to the saturation of phospholipid moieties.

FREMONT-SMITH. Has the phospholipid a protein component?

CLEMENTS. It can be extracted in either form as lipoprotein, which is strongly surface-active, or we can break down the tissue or various extracts from the tissue and take out lipid components, subfractionate these, and demonstrate that the phospholipid subfraction is most strongly surface-active.

Fremont-Smith. In the natural form, when it is functioning, is it part of a protein complex?

Clements. I am assuming that it is, but I don't think we know. One of the questions I was going to pose, after presenting this introductory material, is *how would we know that? What methods could we use to demonstrate this?*

It is a nice problem, because the structure we are talking about is of molecular dimensions, a monomolecular or perhaps at most a bimolecular film. It is readily cast off from the epithelial surface by the ordinary fixation-staining methods. It is of dimensions which can only be properly demonstrated with electron microscopy. Therefore, in order to give a proper answer to the question, one needs to combine new methods of fixation with elegant histochemical methods that can be suitable for electron microscopic study.

Fremont-Smith. Some bacteria have a surface of lipoprotein polysaccharide. I was wondering whether the chemistry of these is similar in any way to the chemistry of the phospholipids in the lung, and whether they are also polysaturated rather than polyunsaturated.

Clements. I can't answer that.

HYPOTHETICAL PATHOGENESIS OF THE RESPIRATORY DISTRESS SYNDROME

Comroe. Dr. Clements, you said that this layer protects the alveoli against collapse of the alveoli and that it also protects against materials in plasma leaking through into an air space. Whenever there is an abnormal lining, would you expect transudation or exudation of some fluid? Those who have tried to explain respiratory distress of the newborn have had two theories: one to explain the collapse, and one to explain the presence of plasma products. Does one theory explain both?

Clements. Are you asking me what I think the pathogenetic sequence of events in respiratory distress is, particularly respiratory distress of the newborn?

Comroe. Yes, any condition in which this monomolecular layer is absent, interfered with, or inactivated.

Clements. At the moment, my prejudices are that the most important events that lead to the pulmonary manifestations are those which interfere with the nutrition of the alveolar cells; that, as a consequence of fetal distress or asphyxia, pulmonary ligation, or bronchus ligation, or administration of 100 percent oxygen at one atmosphere pressure for a long time in experimental animals, alveolar perfusion decreases as a primary event and to such an extent that the alveolar cells, particularly the epithelial cells, are insufficiently supplied and may become "squashy." They fail to produce the phospholipid and the lipoprotein constituents which are necessary for the intracellular plasma barrier and for the external air barrier. If they are not protected against immediate contact with the air-liquid interface, they are more likely to be lysed. This can be demonstrated *in vitro*.

AVERY. Is there any evidence for cell lysis?

CLEMENTS. The evidence is that one can produce surface lysis with naked cells at such interfaces. In this particular situation, or one following fluid instillation and the washing out of surface layers followed by rapid expansion of the lung, one finds evidence of damage to alveolar epithelial cells.

If the barrier function of the cells is interfered with and, as a result of this, permeability to plasma constituents is increased, we have the stage set for accumulation and condensation of fibrin into the hyaline membrane. The physics of the situation, which I think Dr. Comroe meant to bring out, would be that with increased surface tension there would be increased pressure difference between the air space and the lumen of the capillaries acting to promote effusion.

FREMONT-SMITH. Why is the pressure difference changed by the absence of this thin layer?

CLEMENTS. If the surface tension rises in the air space, that is, the retractile tendency of the surface of the lung increases, then, in order to maintain an adequate lung volume, the transpulmonary pressure difference must also increase. When the intrathoracic pressure becomes more negative, the pulmonary circuit becomes a reservoir into which blood dumps from the systemic circuit, and one can then expect distention of the pulmonary capillary bed.

In other words, taking atmospheric pressure as the reference for all other pressures, if the pulmonary capillary pressure with reference to the atmospheric pressure in the air space is raised as compared to the normal gradient, this will tend to push fluid into the air space. If we add that to the evidence that there has been cellular damage and that the barrier function of the intact cells has been interfered with, I think we have two reasons that explain why we see plasma constituents in the air space.

MACLEOD. What evidence do you have that the material you are talking about is not a part of the normal cell wall, since lipoproteins, as far as one knows, are normal constituents of the cell wall in all cells that have been studied? How do you know that you are not extracting the normal lipoprotein components of the cell wall rather than some specialized material that is on the surface?

CLEMENTS. The evidence is not direct. The circumstantial evidence is this: The lipoproteins which we extract from the lungs are not characteristic of the kind of lipoproteins which one generally gets from cell membranes. Secondly, we can harvest this material simply by gentle lavage of the alveolar regions via the airway by a technique which, as far as we can tell, does very little cellular damage; in other words, it does not appreciably extract cytoplasmic constituents. When we use more violent extraction procedures which give access to the inner constituents of the cell, we then get a progressively different composition. In other words, the less deeply the extraction procedure goes into the structure of the lung, the more highly saturated is the fatty acid group in the phospholipids, and the more strongly surface-active is the material. As we go deeper and deeper, we find the kind of lipid composition which characterizes membranes of cells elsewhere in the body.

VILLEE. Is there any corresponding difference in the kind of base attached to the phosphatidic acid: for example, ethanolamine, serine, choline, and so on?

CLEMENTS. Yes. Actually, this is Dr. Avery's and Dr. Klaus's work, and they might wish to comment on this.

We have studied several purified lipids in order to determine their surface activity. What we can say at this point is that only phospholipid materials are capable of strong surface activity, that is, giving a surface tension very nearly zero. Not all phospholipids are capable of doing this. It is only those which contain choline—in other words, the lecithin and sphingomyelin group. Within this group, it is only those substances that have two long hydrocarbon chains that are effective (lyso compounds are not) and among these only those that have saturated fatty acid substituents.

In a word, then, the strongly surface-active material is saturated choline-containing phospholipid. The characteristic which is responsible for the low tension, or at least the requirement determined by examining these materials as monomolecular films, is that they pack into tightly ordered quasi-crystalline structures, with a small molecular area, and this is only possible when the fatty acid chains are saturated. The chains of unsaturates which occur naturally are cis-isomers, are puckered, and will not pack nicely into a monolayer. Sphingomyelin is an exception, since it does contain an unsaturated point. The interesting thing, however, is that natural sphingomyelin contains sphingosine as the trans-isomer, and this chain is only slightly puckered. In spite of the unsaturated point, the sphingomyelin packs to a small molecular area as small, almost, as the totally saturated material.

COMROE. Dr. Avery, did you want to add or subtract something?

AVERY. Dr. Clements has said it very well. I wonder, though, if Dr. Sorokin might comment on the evidence for the source of this material. How certain are we that the septal cell he talked about is synthesizing this compound, and what are the precursors, and what is the turnover rate, and, specifically, how do we go about measuring the turnover rate? All of us have bits of evidence that this cell might be the source, but so far it doesn't add up to a complete picture.

Klaus. There is evidence that the septal cell does participate, but possibly we have argued too long as to whether these unusual cytosomes, sometimes called *lamellar transformations* or *myelin figures,* really come from mitochondria. We should concern ourselves with whether the septal cell is synthesizing the surfactant.

Comroe. You don't mean that we should forget forever which is which but that right now we should settle whether it comes from somewhere in the cell?

Klaus. Then we can observe what happens to the septal cells under various conditions. The evidence supporting the septal cell and its inclusions as being the source of the surfactant are, first, the absence of both the inclusions and strong surface activity in toad and bird lungs, and secondly, the almost complete loss of both inclusion bodies and strong surface activity following bilateral cervical vagotomy in the guinea pig.

Comroe. Why does vagotomy do this?

Klaus. We don't know why the surfactant is diminished. It may be washed away. Possibly, the vagus nerve controls its synthesis.

Dawes. Is the animal still in good condition?

Klaus. No, 4 to 6 hours after the vagotomy, the guinea pig dies with pulmonary edema.

Dawes. What about the dog? The dog will survive bilateral cervical vagotomy.

Avery. He doesn't lose his surfactant activity.

Comroe. I think we should state that when we are talking about surfactant, we are not yet at the stage of extracting a pure substance and weighing it on a balance. We are *measuring the activity* of the material by certain physical tests.

Klaus. By a crude but useful test.

Cross. Why don't birds need this substance? And is this true of all birds?

Klaus. The surface tension measurements were made on pigeon and chicken lungs.[1, 2] In the bird lung, it appears that air passes through the lung into and out of large air sacs. Since there seems to be little change in the internal surface area of the bird lung with respiration, surface tension is not required to change. Not all of the surface properties of the mammalian surfactant are required by the bird.

Cross. Don't they have some alveolar spaces?

Clements. They have air capillaries, don't they?

Sorokin. In birds, respiratory exchange takes place in fine air passages but not in culs-de-sac. Surprisingly, the circulation of air through birds' lungs is imperfectly known. Essentially, air is drawn from a main bronchus into smaller branches (parabronchi), thence through the respiratory capillaries and into postrespiratory air sacs, which are large, dilated chambers without function in respiratory exchange. The air is returned to the main bronchus by another route which bypasses the respiratory surface.[3]

COMROE. We want to give you an opportunity, Dr. Clements, to say what you think are the important things yet to be learned about surfactant. One of these is the precise origin of it. What are the others?

CLEMENTS. One of the important things is the method of estimation. We are talking about making extracts and measuring surface tension, and one is entitled to ask what this has to do with the quantity of a certain substance in the organ and if we think the quantity or quality of that substance might be important in some way to the function of the organ.

This turns out to be, unfortunately, a more complicated situation than we would like, because not only is the measurement of surface tension responsive to the kind of surface-active material and to the quantity of it, but it is also dependent upon the presence of inhibitory or interfering materials. So, if we fail to demonstrate a very low surface tension with an extract, using the saline extraction procedure, which, unfortunately, is well established in the field now, we don't know whether it means a deficiency, an alteration in chemical quality, or an overwhelming amount of inhibitory material.

Unfortunately, we know from *in vitro* experiments that neutral lipids, which are abundant even in the surface-active material itself if added in excess, can interfere. We know that materials which are abundant within the cytoplasm of cells generally, if released in free lipid form, can inhibit it. Therefore, this whole assay becomes more like the measurement of blood clotting. If the blood clots, it's all simple. One can say fibrinogen is present which is acted on by thrombin to form fibrin. But when it does not clot, there are all sorts of reasons why it doesn't.

When we get a low surface tension, we can say we have a stable surface film which will give us a zero tension. Therefore, it must not have been interfered with and there must have been enough of the right kind of material. But when we don't see it, the interpretation is much more complicated.

COMROE. Therefore, what you would really like to have would be two tests—one of activity and one of amount.

CLEMENTS. That's right. At the moment, the closest approach we have to this is to take out the whole lipids of the lung and separate them into a fraction which is strongly surface-active and one which is inhibitory. When we do this, we find that at the time the osmiophilic inclusion bodies appear in the fetal mouse, at the time the saline extract suddenly becomes positive for surfactant, the quantity per gram of tissue of saturated choline-phosphatide rises. The ratio of this to neutral lipids increases even more, and the ratio of saturated to unsaturated fatty acids also rises. This transition from an unstable to a stable kind of lung, which is changed in its morphologic appearance and now shows abundant osmiophilic inclusion bodies in alveolar epithelial cells, has undergone a biochemical change sufficient, I think, to explain the appearance of the strong surface activity in the saline extracts. Similar biochemical events probably also account for the comparable changes in ovine and human fetal lungs late in gestation that Dr. Avery and other workers have observed.

AVERY. I take some comfort from this uncertainty about what we see on a surface balance trough and in our admitted ignorance of all of the chemistry involved in knowing that we have another independent approach to the problem.

We can still look at pressure volume characteristics of excised lungs and see if there is premature closure of units. It seems to me that before grinding up bits of lung, we ought to first determine if the *intact* lung is abnormal. When these two studies have been done concurrently, there is usually a very good correlation.

VILLEE. Have you measured the relative surface tension-lowering effect of the intact lipoprotein versus the free phospholipid?

KLAUS. The lipoprotein has not been isolated in a pure form. Using density gradients, it appears to have density between 1.06 and 1.12, but the impure lipoprotein has a surface tension area diagram similar to lung extract and the free phospholipid. Both the lipoprotein and phospholipid reduce surface tension to 2–3 dynes/cm when the surface is compressed.[4, 5]

VILLEE. Is that comparison made using the number of milligrams of phosphorus, the milligrams of total material, or something else? What is the denominator there?

KLAUS. The free phospholipid requires a monolayer on the surface. The exact amount of lipoprotein required has not been determined.

SEGAL. Do temperature changes, either in the lung of the baby or in the fluid in the trough, have any material effect on the measurements as made in the trough or upon the interpretation of these measurements?

CLEMENTS. The temperature at which the measurement is made is not very important if one keeps it in the range between ordinary room temperature and normal body temperature, that is, between 27° C. and 37° C. However, one has only to raise the temperature a few degrees centigrade to completely spoil everything. If, for example, measurements are made at 45° C. or 46° C., it becomes practically impossible to tell the difference between an extract of healthy, fresh experimental lung and one with extensive atelectasis and hyaline-membrane formation. This has to do with the kinetic properties of the molecules in the surface film. We have studied this systematically, and it follows predictions of kinetic theory very nicely.

COMROE. Does the temperature of the fetus ever get high enough to change the activity of the surface film?

CLEMENTS. It seems to me there are a number of ways in which temperature might affect the film *in vivo:* by changing the circulatory pattern, by affecting the metabolism of the cells and substrate utilization relationships, as well as directly affecting the physical properties of the surface film.

AVERY. We need to know more about the circulation that Dr. Clements said brings the nutrition to the alveolar cell. What is the bronchial circulation in the fetus? Does it ever get anywhere near an alveolus, or does the pulmonary artery circulation nourish an alveolar cell in the developing lung?

COMROE. In the adult, whenever there is a deficient pulmonary circulation, the bronchial circulation enlarges. You really want to know whether there is an enlarged circulation going to the alveoli in the fetus?

AVERY. Yes. And what part of the fetal lung is getting its nutrition from systemic flow and what part from pulmonary artery flow? How good are the numbers we all quote, originally from the work of Dr. Dawes? [6] Is it only the lamb, or do all species have only 10 percent of the cardiac output going through the pulmonary artery in the fetal stages?

DAWES. The data were based on a mean of six fetal lambs.

COMROE. None of them had respiratory distress, did they?

DAWES. No. They were unventilated.

SEGAL. I think, in partial reply to Dr. Avery's question, Karl Pump,[7] at the University of British Columbia, has shown by injection studies that there is some shunting or anastomotic mechanism between the two circulations in adult lungs.

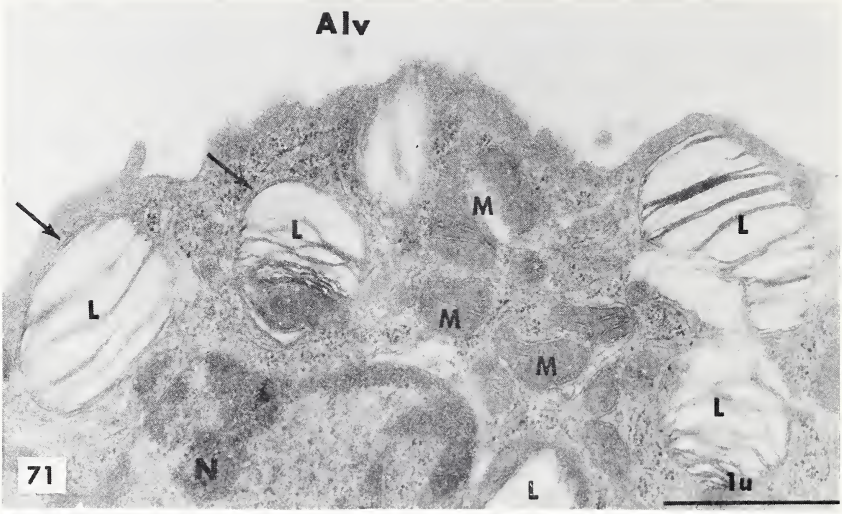
ALWAY. Has any change been noted in the distribution, quality, or quantity in the osmiophilic bodies in so-called healthy and unhealthy lungs?

KLAUS. This has been examined following bilateral cervical vagotomy in the guinea pig. When the surfactant is diminished, the osmiophilic bodies are almost completely lost.

AVERY. There is another condition in which the inclusions can be altered which might be related to the alveolar lining layer.[8]

Figure 71 is an electron micrograph of a control adult guinea pig lung, showing the same sorts of bodies that Dr. Sorokin demonstrated earlier. Other guinea pigs were exposed to 15 percent carbon dioxide in air for 24 hours. They developed respiratory acidosis, respiratory distress, and were sacrificed.

The osmiophilic-staining materials are gone, and there are just vacuoles in that lung (fig. 72). This is a reversible injury. However, at this point there is no detectable surface activity by our method of detection. When the osmiophilic material returns, we are able to detect the surface-active material.



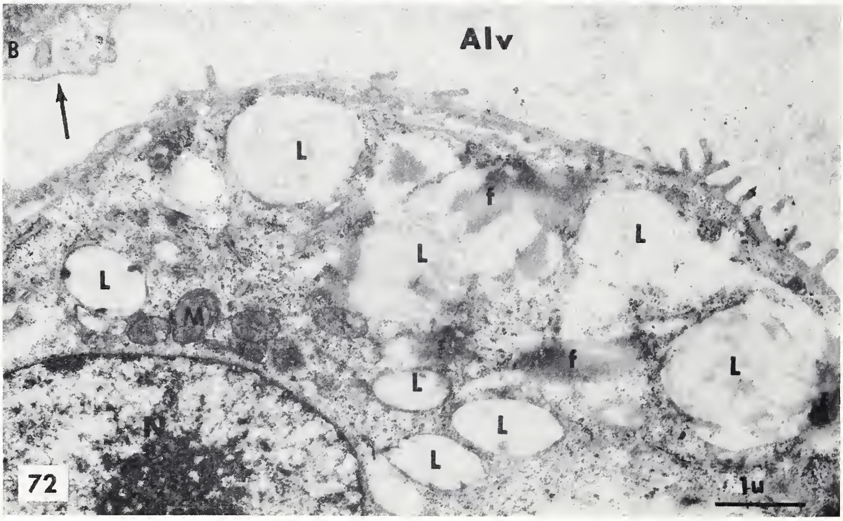


FIGURE 71.—Control animal. Part of a granular pneumocyte with six lamellar bodies. Several of these exhibit an outer double membrane (*arrows*), indicative of their mitochondrial origin. Mitochondria are designated M, the nucleus N, and the aveolar air space Alv. X 27,000. (Reproduced by courtesy of Dr. K. Bensch, Department of Pathology, Yale University Medical School.)

FIGURE 72.—Part of a granular pneumocyte after continuous (24 hours) exposure to a 15 percent CO_2 atmosphere. The considerably enlarged lamellar bodies (L) are without their lamellae but contain within a very electron-translucent matrix a network of moderately electron-opaque material. Accumulations of lipid (f) are present in several lamellar bodies. Mitochondria (M), nucleus (N). The aveolar space (Alv) is filled with edema fluid. The left upper corner of the photograph is occupied by parts of the swollen cytoplasm of a membraneous pneumocyte (*arrow*). Basement membrane (B). X 13,000. (Reproduced by courtesy of Dr. K. Bensch, Department of Pathology, Yale University Medical School.)

Stahlman. What were the pH values?

Avery. About 7.1. The pCO_2's were of the order of 100 mm Hg.

Comroe. Is this an anesthetized guinea pig?

Avery. No.

Comroe. Doesn't the 15 percent CO_2 anesthetize the guinea pig? In high concentrations, CO_2 is a narcotic.

Avery. No, they are breathing rather deeply, and sometimes they gasp. Guinea pigs and rats are not anesthetized by CO_2 until the concentration is above 20 percent. They look sick during the uncompensated phase of the respiratory acidosis.

Fremont-Smith. Do they have pulmonary edema?

Avery. Yes, and atelectasis and hyaline membranes under the light microscope.

Oliver. Dr. Avery, was the remaining mixture air or oxygen?

Avery. Air and 15 percent CO_2.

Karlberg. May I come back to the question that Dr. Avery brought up? What is known about the turnover of the surface-active material? You described a situation where the material disappeared in 24 hours.

Avery. We have been studying the turnover by very indirect methods for the past couple of years. With certain insults, such as inspired carbon dioxide, and probably with pulmonary artery ligation or the equivalent diminution in pulmonary blood flow from induced pneumothorax in rabbits with atelectasis, it is about 24 hours before the ability to detect this material on the surface balance is lost. Under other situations, it can be very much quicker. Dr. Sami Said, for instance, has shown that by inducing pulmonary edema in an animal with an infusion of dextran mixtures, overloading the circulation will result in absence of this material from the lung within 10 minutes. Therefore, I gather, in certain situations, inhibitors can be released or in some way make it impossible to detect the surfactant.

Klaus. The surfactant is first noted to be altered 18 to 24 hours after unilateral pulmonary artery occlusion.

Avery. Does surfactant reappear after pulmonary artery occlusion?

Clements. Dr. Tooley[9] has shown it to be reversible over a very long time course. There is a lag period following the occlusion of the artery during which one continues to demonstrate strongly surface-active material by the saline method of extraction; by 24 hours, a definite change has occurred. For the following 4 to 6 weeks, the saline extracts are abnormal.

Avery. When do you untie the artery—at 48 hours?

Clements. The animal unties the artery for you, because in this situation, if he has been sterilized with antibiotics and is in good condition and he gets an incomplete infarction, a profuse collateral circulation develops from the bronchial system. After 4 to 6 weeks, the alveolar regions become well perfused again, as shown by nitrous oxide uptake or carbon dioxide elimination. The lung histology returns very nearly to normal, and the saline extract is again normal. The lung is 80 to 90 percent functional again for carbon dioxide elimination but not for oxygen uptake, because its perfusion is from the systemic circuit. This is another situation which I think illustrates the correlation between what is measured in the saline extracts, the mechanical properties of the lungs, and the morphologic studies.

COMROE. I think the function of this group at the moment is to ask people in the different disciplines whether there are any particular questions that would be of value to those working in the field, or whether there are any suggestions for future research from people who have not been thinking about this too much before.

OLIVER. Is there additional information regarding either interfering substances or inhibitors? Dr. Clements has suggested neutral lipids and prolonged exposure to high oxygen tension, and Dr. Avery, high pCO_2 and low pH. Are there other substances that might affect surface tension?

KARLBERG. What about metabolic acidosis? Is there any difference between metabolic acidosis and respiratory acidosis?

COMROE. Are there any other suggestions or questions?

LEVINE. In premature babies who die of the hyaline syndrome or idiopathic respiratory syndrome, do you see osmiophilic cells? What is the cytochemistry of the lung when seen by electron microscopy?

AVERY. Dr. Campiche[10] has reported that the number of osmiophilic inclusions per cell are decreased. The alveolar cell itself is fragmentary and disrupted under the membrane but not necessarily uniformly so. However, I don't think we know enough about this. It is difficult to get electron microscopy from human lungs without doing biopsies and this hasn't been done. These conclusions are based on very few samples from Dr. Campiche.

VILLEE. I would like to ask how you can be sure that the situation in the adult guinea pig is comparable to the situation in the premature infant with respect to this surfactant material.

AVERY. I have no assurance that it is comparable.

CLEMENTS. We ought to say a little more than that. Comparing the lipid fractions of normal lungs and of a few that contained hyaline membranes, we have found that the total lipid content was somewhat diminished, but that the amount of saturated choline-phosphatides was much decreased, to as little as one-hundredth of the normal quantity. Thus, the ratio of strongly surface-active compounds to inhibitory lipids was strikingly lower in specimens from cases of respiratory distress with hyaline-membrane formation. We have not yet performed these assays on vagotomized guinea pigs.

VILLEE. What fraction of the total lipid of the lung is represented by the surface-active lipids?

CLEMENTS. The surface-active lipids make up approximately 5 mg/gm of tissue wet weight as compared to approximately 40 mg total lipid per gram of tissue wet weight.

FETAL LUNG FLUID

Comroe. I would like to ask an entirely different question. How much fluid is there in the lung of the fetus—in the airway, in the alveolar ducts, and in the alveoli—just as it is about to be born, and where does this fluid go?

Dawes. Isn't the question, really, where it comes from?

Comroe. We'll have to come back to that later on. First, we should find out how much there is.

Dawes. It depends on whether the baby inhaled before it was born.

Cook. The water content increases with gestational age, presumably because there is an increasing amount of fluid in the alveolar spaces (fig. 73). Interstitial fluid probably does not increase, but we do not know this for sure.

Cross. This is opposite in direction from the water content of the whole fetus, is it not?

Cook. Yes, the other tissues of the fetus have a decreasing water content as the organism becomes more mature.

Figure 74 shows the effect of respiration on the water content of the lung. These few data suggest that it takes up to 10 minutes before the

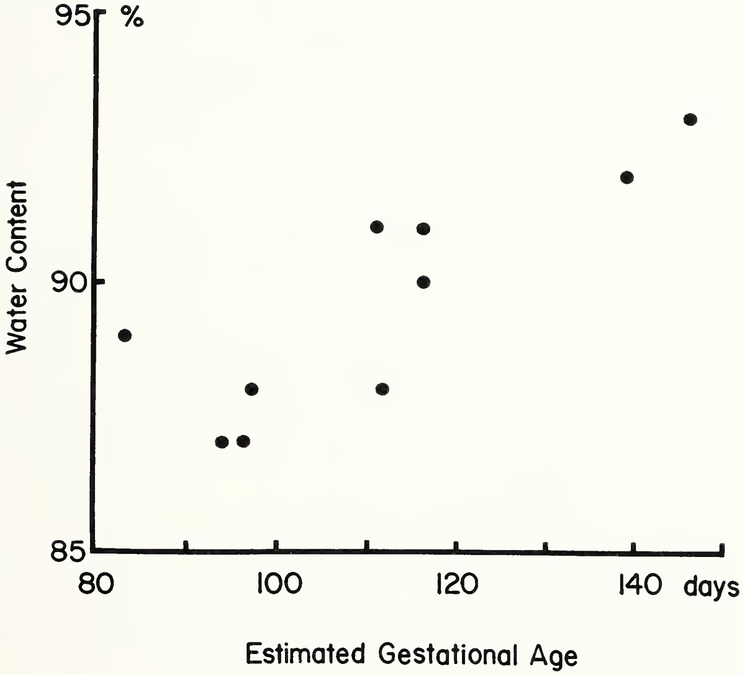


Figure 73.—Water content of lungs expressed as percent of total weight for stillborn lambs of varying gestational age. All animals delivered by cesarean section and trachea clamped immediately. (Reproduced by courtesy of Dr. M. M. Orzalesi, et al.)

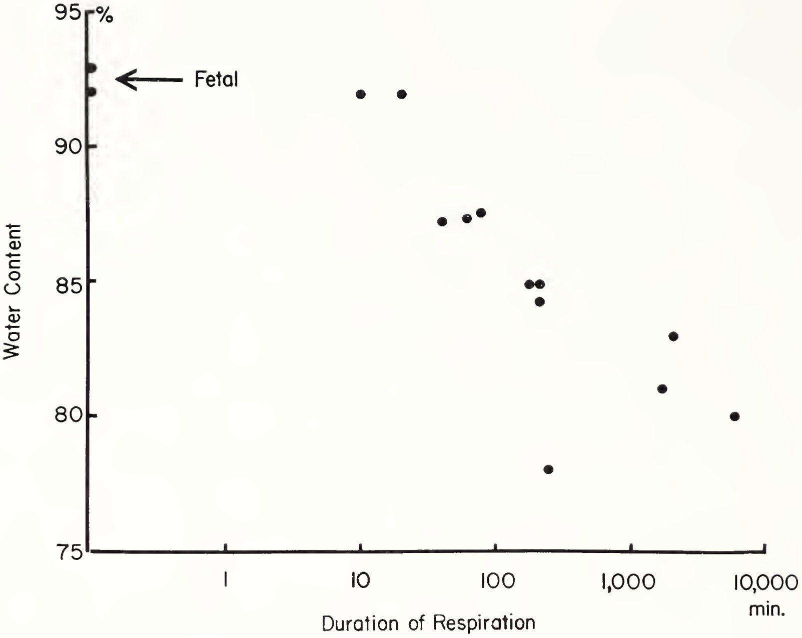


Figure 74.—Water content of lungs expressed as percent of total weight for liveborn animals sacrificed at varying periods after the onset of respiration. (Reproduced by courtesy of Dr. M. M. Orzalesi, et al.)

fluid content begins to decrease appreciably. If the fluid really remains that long, it is surprising that bubbles and foam are not produced.

Comroe. Since you have not sectioned these lungs and found whether the fluid is in the airways, in the alveoli, or in the tissue, a slow disappearance might mean that it is edema in the tissue rather than in the alveoli.

Cook. This is possible, although previous experiments on pulmonary edema in adult dogs suggested that an increase of 10 or 20 percent in the lung weight due to pulmonary edema resulted in profound changes in the mechanical properties of the lung.[11] I doubt that much of this fetal "pulmonary" fluid is interstitial.

Comroe. Is this a huge amount for the lung?

Cook. The lung weight decreases by approximately 50 percent after several hours of respiration.

Fremont-Smith. Have you determined the chemical composition?

Cook. No.

Fremont-Smith. Is it amniotic fluid?

Cook. Although part may result from aspiration of amniotic fluid and some of the amniotic fluid may result from tracheal fluid, the two are different in their gross character.

DAWES. Dr. Ross[12] has measured the osmolarity of the fluid draining from the lungs of a fetal lamb. It is close to that of plasma and much greater than that of amniotic fluid. Hence, the fluid in the bronchial tree of a lamb which has not inhaled is not amniotic fluid.

AVERY. Do you mean that if the glottis is open *in utero* and the respiratory tract is essentially a continuous container, there is fluid of one osmolarity at one part of the tract and fluid of another osmolarity in another part?

DAWES. I assume this is so. I would guess that the lung is continually producing a very small quantity of fluid. We know that if you do a tracheotomy on a fetal lamb and continuously drain fluid from it during a long experiment, fluid does continue to accumulate. We know from Jost's experiments[13] that when the neck of a fetal rabbit is tied *in utero,* the potential air spaces of the lung become distended with fluid.

I think there is little doubt, therefore, that the fetal lung does continually produce some fluid, perhaps in rather small amounts, and that this moves down and eventually mixes with the amniotic fluid.

COMROE. Is it formed by secretion or filtration?

DAWES. I do not know, but it is likely to be a combination of both, because there are secretory cells in the tracheobronchial tree.

OLIVER. There is evidence that the fluid is secreted, at least in part, by the lung, from work reported by Adams and coworkers.[14] They simultaneously collected arterial blood from the ewe, umbilical vein, fetal tracheal fluid, and amniotic fluid. The chemistries are sufficiently different to conclude that tracheal fluid is secreted rather than a plasma filtrate.

SEGAL. This was continuous production of respiratory tract fluid and not just a spot sample. It was collected over a period of hours.

COOK. The tracheal fluid of the lamb is surface-active, whereas amniotic fluid is not.

I would like to make one point about the apparent continuous production of fluid from the lung. Our observations in lambs suggest that, if there is no differential in the pressure of the tracheal fluid in relation to atmospheric pressure, there is no large outflow of fluid.

COMROE. You don't need much of a pressure differential to make fluid flow, and over a period of time you can have large quantities with small differential pressures.

COOK. But do you believe that flow is going on at this rate all the time *in utero*?

COMROE. I don't know how you could measure a small pressure difference between these two points and say there was no pressure difference. What were the rates of flow?

OLIVER. They were in the order of 1 to 2 ml per minute.

CLEMENTS. Over many hours. This represented something like half the body weight of the fetus.

KARLBERG. How high is the pressure *in utero* in the ewe? In human beings, it is something around 20 cm of water. The fetus inside is at a certain pressure *in utero*, and then it is lifted out.

CALDEYRO-BARCIA. In the pregnant human uterus, the tonus, that is, the amniotic pressure between contractions ranges from 4 to 8 mm Hg until the eighth month of pregnancy.

COMROE. Why did you ask, Dr. Karlberg?

KARLBERG. I asked because we were discussing the rate of flow of this fluid. *In utero*, the fetus is under a certain pressure which is also transferred to the tracheobronchial tree. When the fetus is moved out, the pressure will drop to that of the atmospheric pressure. Will this pressure change alter the circulation and the distribution of blood between the placenta and the fetus with the placenta still being *in utero*?

CLEMENTS. Dr. Dawes, may I ask how high the fluid rises in the manometer?

DAWES. It does not rise very high, a few centimeters of water or a little more.

CLEMENTS. Where does it rise? With respect to what level?

DAWES. With respect to the chest level.

CLEMENTS. Then, this is the fetus outside?

DAWES. Yes. The fetal chest is filled with fluid.

If the trachea is cannulated and the cannula closed, then, over a period of about an hour the arterial pressure of the fetus begins to fall. When the tracheal cannula is opened, a large quantity of fluid flows out and the arterial pressure returns to its initial value. I infer from this that accumulation of fluid within the lung can be sufficient to impede venous return and reduce cardiac output. Nowadays, if we want to occlude the trachea so the fetus cannot inhale air, we attach the tracheal cannula to a fluid-filled bag.

POTTER. Because of the work of Dr. Franklin Snyder who has carefully studied the effects on the rabbit fetus of various drugs and chemicals in relation to respiratory movements of fetuses delivered into a waterbath but with placental circulation still intact, Dr. Davis and I [15] put thorotrast, which is a radiopaque emulsion, into the amniotic sac.

When a therapeutic abortion was performed by cesarean section immediately after injecting thorotrast, nothing could be demonstrated in the fetal lungs, either on X-ray or microscopic examination, but if there was an interval of more than 12 hours, this material was always found within the potential air spaces.

We put thorotrast into the amniotic sacs of 12 fetuses. The smallest fetus weighed 39 gm, the largest 440 gm. All were examined by X-ray immediately after removal from the uterus, and sections of the lungs were later examined microscopically. Both types of examination showed the potential air spaces to be filled with thorotrast. The material in unconcentrated form is not visible in this amount on X-ray, so in order to be visible, fluid must have been absorbed and the emulsion concentrated in the lungs.

In the experiments of nature, where a fetus did not have a head, where the trachea was occluded, or particularly where it had sequestered lobes, these invariably do show distended spaces. However, the lungs are not normally developed.

Furthermore, in babies who have bilateral renal agenesis (I have now performed autopsies on 50 such infants, and in none was amniotic fluid known to be present), there are varying degrees of failure of maturation of the lung. In some, there is almost no development beyond the most primitive stage, and the lungs are composed almost entirely of tubular structures with complete lack of alveoli. In others, there is some maturation, but the reason these infants die within the first hours is because they do not have enough lung tissue to support an extrauterine existence. I assume one could argue that this is a second abnormality which is coincidental with the abnormality of the kidneys, or that a single underlying cause is responsible both for the lack of kidney formation and the lack of pulmonary development. It is tempting to conclude, however, that the absence of the kidneys is responsible for the lack of amniotic fluid, and this in turn is responsible for the lack of lung development.

Pulmonary hypoplasia occurs in anencephalic monsters who have spinal rachischisis and in babies with large diaphragmatic hernias, in both of which there is insufficient room for development. They, too, have a marked inhibition of normal pulmonary development but never to the degree of those with renal agenesis. In our interpretation of where amniotic fluid comes from and where the material within the potential air spaces comes from, I think we must take cognizance of nature's experiments and we must not assume, as a result of a single experiment, that we have the answer to the total problem.

We also injected thorotrast into the amniotic fluid in 10 infants at the time of delivery by cesarean section, and the material was demonstrated by X-ray in the lungs of all of them. They were perfectly normal infants; they breathed immediately, spontaneously, and behaved perfectly normally.

AVERY. Then, we can say with certainty that that degree of inhalation of amniotic fluid was not life-threatening, nor did it make the infants sick.

VILLEE. Dr. Potter, I am wondering whether the radiopaque material could have entered the lungs by way of the gastrointestinal tract and the circulatory system.

POTTER. I think, in the short length of time that elapsed, it would be impossible even if it were absorbable. It is also more concentrated in the bronchi and in the bronchial tree than it is in the rest of the lung tissue.

Smith. Surely, the squamous cells in the alveoli of newborn babies who die of other causes do not get there from the gastrointestinal tract.

Potter. I think that everybody agrees that when asphyxiated, all fetuses inhale amniotic fluid.

Smith. I don't think they always die.

Potter. That's right. In many infants who die 6 weeks, even 6 months, after birth, epithelial cells from the amniotic fluid may be found within alveoli.

Ramsey. What is the significance of the time lapse before thorotrast is found?

Potter. I think there is absorption of water and concentration of the emulsion. Water has been shown to be absorbed very rapidly out of the capillary system in the lungs. If one is using, as an argument against the fluid in the lungs being of amniotic origin, the fact that amniotic fluid in the lungs ought to interfere with respiration, this is completely invalid. First of all, the space occupied by fluid is very small in relation to what the space becomes when occupied by air, and, secondly, the fluid can be very quickly absorbed.

Comroe. Water is very quickly absorbed, but large molecules of proteins and plasma are very slowly absorbed over a period of 3 or 4 days. But if this is amniotic fluid, it is much more closely related to water than to plasma.

James. It may not be reasonable to conclude that the rate of absorption in newborn animals, where the pulmonary pressure is relatively high, is the same as the rate in adult animals in whom the pulmonary artery pressure is lower than colloidal oncotic pressure of the plasma.

Schafer. There is another possible experimental approach to the study of this problem. A large amount of literature is available on the teratogenic effects on the embryo of drugs, chemicals, biological and physical agents when administered to the maternal organism during various stages of gestation. Selective malformations can be experimentally produced in the fetus of the mouse and rat that are associated with either increased or decreased amniotic fluid volume. The role of amniotic fluid volume on the development of the lungs and other organs might be studied in these preparations.

Comroe. Which specific ones would you want to think about? Would you want an animal with no trachea?

Schafer. I think I would be interested, first of all, in an embryo with no kidneys. For example, urinary tract anomalies have been produced in two-thirds of rat embryos following administration of pteroylglutamic acid (PGA) to the mothers. There are also certain strains of mice in which one finds deletion of organs. Dr. Gluecksohn-Schoenheimer [16] described severe disturbances of the urogenital system in Danforth short-tail (Sd/+) mice.

In approximately one-third of the heterozygote newborns, the kidneys failed to form.

ALWAY. In normal circumstances, what is the history of the quantity of amniotic fluid in relation to gestational age?

BRUNS. Elliott and Inman [17] reported the volume to be maximal (1,000 ml) at 38 weeks of pregnancy. After this it declines at a rate of 145 ml per week until by 43 weeks it is about 250 ml. Amniotic fluid volumes have been measured in early pregnancy by a number of investigators. However, there are few data on amniotic fluid volumes between the 25th and 35th weeks of normal pregnancy. In the rabbit, the volume of amniotic fluid increases until about the 26th day, when it rapidly diminishes from a mean of 4.5 ml to 0.75 ml at the 30th day of gestation. In the guinea pig and cat, the amniotic fluid increases until birth, indicating some species difference.[18–20]

RAMSEY. Is this absolute volume or volume in proportion to the size of the fetus?

BRUNS. In the human being, amniotic fluid volume is indistinctly related to birth weight. According to a group from England, the relationship is biphasic. Birth weights of 3,750 gm are associated with the largest amniotic fluid volumes. An increase or decrease in birth weight is accompanied by a considerable decrease in amniotic fluid volume.

RAMSEY. I ask that, because I am sure that Dr. Caldeyro will confirm the fact that there is relatively less amniotic fluid in the monkey at term than in the human.

POTTER. Proportionately, there is more amniotic fluid at 16 to 20 weeks than at any other time.

RAMSEY. Even in the human?

POTTER. Yes. Certain types of polycystic kidneys are also associated with lack of amniotic fluid, and in these one sees the same type of pulmonary hypoplasia that is associated with the renal agenesis.

COMROE. But do you ever see an abnormality in which there are no kidneys and good lungs?

POTTER. No, I never have.

COMROE. Well, lungs that had alveoli?

POTTER. As I mentioned, there is a great variation in the degree of differentiation of the lungs. In some, you do find some alveolar development, but the lungs are always small and in many instances they have very few alveoli.

DAWES. There is the problem about material of this kind, whether failure of development of the lung results, not from failure of kidney development, but as an associated defect. Perhaps the kidneys could be removed at an early age of gestation?

COMROE. Is the kidney function of any use to the fetus?

DAWES. Insofar as it produces amniotic fluid.

Comroe. If there were no kidneys, would anything accumulate in the fetus that might interfere with the development of other organs?

Silverman. What about acquired oligohydramnios as a result of leak? Is this associated with pulmonary hypoplasia?

Potter. No, but such a condition occurs late in pregnancy and is not associated with complete absence of amniotic fluid.

Comroe. The vital matter is whether the fluid in the lungs comes from one, two, three, or four sources. At the moment, the evidence seems to show that it comes from multiple sources.

RESPIRATORY DISTRESS SYNDROME IN MONKEYS

Aldrich. Dr. Pickering, does the respiratory distress syndrome, as seen in human beings, occur simultaneously in any of the subprimate species you have been studying for so many years?

Pickering. Yes, it does, and in a manner quite the same as that seen in the human being.

Comroe. In what species?

Pickering. In Macaca mulatta monkeys.

Comroe. How often do you see it? Do you know anything about its origin or pathogenesis?

Pickering. Postmaturity is one factor which is common. The postmaturity syndrome is associated with a spectrum of problems, one of which is atelectasis. There are also some among the group with a hyaline-membranelike disease. There also appears to be a high incidence of central nervous system damage in these infants. Postmature infants weigh less than those delivered at normal term plus or minus 10 days. Moreover, they frequently have moderate jaundice and discolored skin. They eat poorly and do not thrive nearly so well as infants who are delivered at the expected time. Prolonged gestation, defined as delivery of an infant 10 days or more beyond the mean normal age at parturition—167 days—has occurred with an incidence of 6 percent in the past 120 deliveries to normal females in my colony. The same incidence was found for prematurity. Respiratory distress also appears in infants which we have delivered by cesarean section as prematures.

Comroe. What is your autopsy rate?

Pickering. One hundred percent.

Dawes. Of 43 fetal monkeys which were asphyxiated at birth, after delivery by cesarean section under local anesthesia, 21 developed respiratory distress. The incidence was particularly high in monkeys which weighed less than 400 gm at birth. The numbers quoted include instances of frank pulmonary edema as well as respiratory distress (table 1).

Table 1.—*Incidence of respiratory complications in monkeys delivered by cesarean section*

Weight in grams	Asphyxiated on delivery	Not asphyxiated
>500	5/13	0/5
400–500	7/17	0/15
<400	9/13	2/7

Reprinted, by permission, from Adamsons, K, et al: Resuscitation by positive pressure ventilation and Tris-hydroxymethylaminomethane of Rhesus monkeys asphyxiated at birth. *J Pediat 65*: *807–818, 1964* (The C. V. Mosby Co., publishers).

Windle* has found a very low incidence of respiratory distress in monkeys delivered by cesarean section under local anesthesia *without* asphyxia, although only 2 out of 20 monkeys weighed less than 400 gm at birth.

Pickering. In the fetal monkey, there is a far greater spread in body weight than there is in relative maturity. Therefore, when one considers the use of this animal as an experimental model for human problems it is much more important to know the true conception age rather than to rely on birth weight.

Dawes. We know the gestational ages of the great majority of the monkeys studied. Dr. Caldeyro's experiments were done with the use of general anesthesia and involved an extensive preparation.

Caldeyro-Barcia. The conditions of our experiments are not comparable at all with those of Dr. Dawes. Our animals received anesthesia or analgesia for several hours, and many catheters and electrodes were inserted in the mother and in the fetus.

Dawes. To summarize the situation, the spontaneous incidence of respiratory distress in the Rhesus monkey is very low, even after premature delivery. It is much increased by asphyxia at birth.

Comroe. Then, essentially, the question is, "Is there an experimental animal in which this might be studied?" And the answer is yes.

INITIATION AND CONTINUATION OF RESPIRATION

Dawes. A lot of attention has been directed to the first breath, but the more interesting question may be, "Why does breathing continue?"

The unanesthetized fetus, the Rhesus monkey *in utero* or the lamb delivered from its mother (using spinal or local anesthesia) but still attached by an intact umbilical cord, does not breathe. The arterial pO_2 is 20 to 35 mm Hg and the pCO_2 from 35 to 45 mm Hg, varying according to whether the mother has or has not been hyperventilating. If the umbilical cord is then tied, the monkey or lamb starts breathing, and an hour or two later is breathing normally and rhythmically with an arterial pCO_2 of 35 to 45 mm Hg and a pO_2 of 70 to 80 mm Hg. It is evident that something other than a high pCO_2 or a low pO_2 must be acting to keep the baby breathing.

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*W. F. Windle: Personal communication.

When a lamb or monkey is delivered by cesarean section and the cord is tied, nothing happens for 30 to 45 seconds. Then, the animal starts to make regular respiratory movements and, if allowed to inhale air, it starts to breathe spasmodically and, eventually, rhythmically. I suppose all of us would agree that this is very likely due to the excitation of the systemic arterial chemoreceptors by the asphyxia caused by tying the cord. This is the obvious explanation of why a baby starts breathing. What we now have to explain is why it continues to breathe. There are several possible explanations. I have evidence on only one, and that is *cooling*. If you deliver a lamb under local or general anesthesia, still attached by the umbilical cord to the mother, and cool it so that the rectal temperature drops by 2° C. or 3° C., it begins to make quiet, regular respiratory movements. It does not gasp. If the trachea is cannulated, small volumes of fluid wash in and out with each movement. There is no significant change in arterial pO_2 or pCO_2. If you play a fan on the lamb to cool it, under appropriate circumstances the lamb will stop making respiratory movements when the fan is switched off but will begin again as soon as it is switched on.

SMITH. Is the cord circulation interrupted?

DAWES. The cord is intact and the fetus receives O_2 and gets rid of CO_2 through the placenta only. The trachea is cannulated and filled with fluid. The Hering-Breuer reflexes can be demonstrated. When intratracheal fluid pressure is raised, the respiratory movements become slower. When it is lowered, they become more rapid. Both phenomena are abolished by cutting the cervical vagi. Cooling therefore is one stimulus which excites quiet, rhythmic respiratory movements in the otherwise intact fetus.

COOK. How do you know it is the cooling and not the fanning that is doing this?

DAWES. We left the fan running till the lamb's skin was dry. The respiratory efforts died away and ceased. When the skin was wetted again, they started once more.

SILVERMAN. When you say the temperature dropped 2° C., do you mean the skin temperature?

DAWES. No, the rectal temperature. We originally made this observation by accident. We wished to see whether fetal O_2 consumption would increase in a fetal lamb when it was exposed to cold. The first thing that happened was that the lamb began to shiver violently and then started to make respiratory movements.

COMROE. Since Keatinge[21] is at Oxford, I am sure you know of his work. He found that a cold shower increased ventilation tremendously in adult man. This came on instantaneously and therefore it must have been a reflex. It was not due to anticipation of the event.

KARLBERG. I have made similar observations with normal newborn infants delivered by cesarean section. Once when I was the pediatrician-in-charge and everything was going all right and nothing special had to be done, the midwife and I decided, "Why not wash the baby immediately?" So we did. The nicely breathing baby, only 4 or 5 minutes old, was immersed up to the neck in warm water, about 36° C. The baby stopped breathing. I removed the baby and it started to breathe again. I repeated the procedure twice with the same effect, but I was not allowed by the midwife to do this again. Since that time, I have done the same thing with two other babies, and they behaved in a similar manner. I haven't had the opportunity, however, to follow the blood gases during such a procedure.

CROSS. I have seen the same thing happen in heating a premature baby.

COMROE. With hot air or hot water?

CROSS. Air. By rapidly increasing the temperature, the infant stopped breathing. This could be very important from the point of view of nursing babies.

DAWES. We have seen the same thing in two lambs delivered under local anesthesia. Some hours later they were warmed either by immersion in warm water or by radiant heat, and suddenly they stopped breathing. In one of these lambs we were measuring his tidal air and O_2 consumption when breathing slowed, tidal air decreased, breathing stopped, and the lamb turned blue and convulsed. Normal breathing was restored by cooling. This sequence of events was repeated three times on this lamb.

COMROE. I think that pediatricians have known about sensory stimulation for a long time. My guess is that this matter of cold water or fanning is simply one of many stimuli which can flow into the central nervous system and cause excitation of centers. Ice water is a very dramatic one for man, but there are many other aspects of this.

Nathan and Sears[22] showed that if you cut the sensory nerves coming from particular respiratory muscles of man, these muscles quit contracting for a week or a month and then gradually start to contract again. Sears has recently been working with Eccles, and they have shown that the spindle of the respiratory muscle seems to have the capacity to excite the spinal cord and to make impulses coming from the centers much more effective than they would be without any sensory input from the muscle. This, then, may be another way in which an animal, once it starts breathing, keeps breathing—by sensory input from its own respiratory muscles.

The reticular activating system, I am sure, is also important, to judge from all of the studies on awake, asleep, and anesthetized man. The responses are quite different in these different situations. I believe there must be many types of sensory input to the central nervous system which help keep breathing going once it has started.

I would like to ask this question, Dr. Dawes: Some people believe and, I guess, have pretty good evidence, that one can completely deafferentate the medulla of an adult animal, and breathing continues in a somewhat rhythmic fashion, or at least it continues. Do you know whether this happens in the newborn?

DAWES. No, I don't. Dr. Comroe, these comments are extremely interesting, because they suggest there aren't factors other than cold in the newborn infant as you suggested there might be.

COMROE. Spanking does it, doesn't it?

DAWES. True, but under natural conditions it now looks as if you can stop breathing in a newborn baby or animal by rapid warming. That would mean that the missing factor is cooling and nothing else.

COMROE. What in the world happens to babies that are born in the tropics?

OLIVER. We have measured the change in body temperature after birth and studied three groups of term babies (fig. 75).[23]

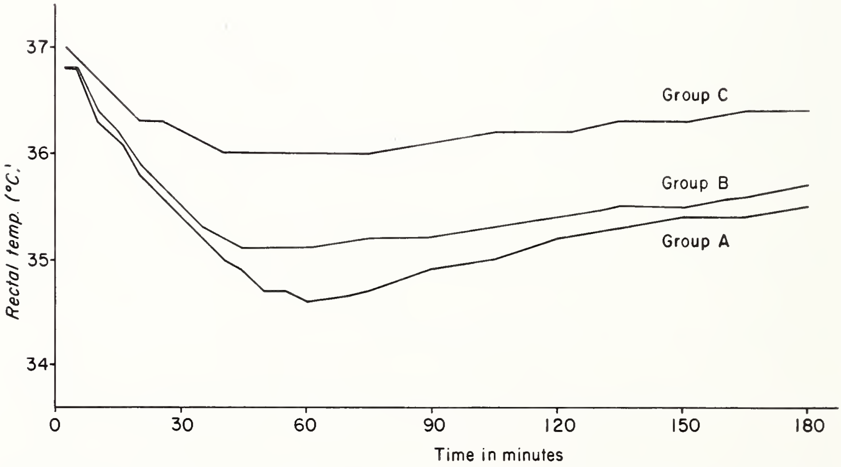

FIGURE 75.—Mean core temperatures in term infants beginning at birth with differing environmental conditions. (See text for details.) Reprinted, by permission, from Miller, D. L., and Oliver, T. K., Jr.: Body temperature in the immediate neonatal period: The effect of reducing thermal losses. *Amer J Obstet Gynec,* to be published.

Deep body temperature, beginning 2 minutes after birth, was recorded from a thermocouple inserted about 9 cm into the rectum. The babies in groups A and B were treated similarly in an air-conditioned, cool (average 21° C.) delivery room; namely, they were put into a warmed but open crib and were kept more or less covered. The group A babies, when they arrived in the nursery at about 40 minutes, were bathed in a 3 percent hexachlorophene solution at lukewarm temperatures, a custom being carried out in many nurseries. This procedure caused a still greater drop in body temperature.

In contrast, a third group (C) of babies were placed into an incubator with the air temperature set between 34° C. and 35° C., at 50 percent humidity at 2 to 3 minutes of age. This might correspond to the group born in the tropics. Despite the fact that they were put into such an environment, you can see that there is still a drop in body temperature to about 36° C. because, being wet, they have considerable evaporative heat loss. This is significantly less than the other two groups, and the return to normal occurred more rapidly in this group. There was no evidence of hypoventilation in the group C babies, but they were not rapidly rewarmed.

While we agree that infants should not be rewarmed quickly, it is our belief that a fall in body temperature, as occurred in the group A and B babies, should likewise not be permitted because of the biochemical effects described by Dr. Gandy et al,[24] which we have confirmed.

How fast was the infant who became apneic warmed, Dr. Cross?

Cross. The air, which was fairly dry, was increased from 28° C. to 38° C. in about 6 minutes. I can't give you the precise body temperature, but it would have been about 35° C. or 36° C. I would emphasize that our air was dry. Pediatricians generally have their incubators highly humidified, and 36° C. dry is very different from 36° C. wet. We have no precise information for the baby as to the equivalent temperature at 100 percent humidity.

James. Dr. Cross, how long after starting the hot air did the babies begin to hypoventilate, or did they actually stop breathing?

Cross. We weren't measuring breathing at this time.

James. Could the apnea have been the result of hyperventilation during exposure to cold? This stimulus causes the infant to hyperventilate, and he may lower his pCO_2 by as much as 21 mm Hg.[24]

Cross. Part of the hyperventilation is because his metabolic rate has gone up.

James. I agree. In the cold environment he will develop a metabolic acidosis. The healthy infant compensates for this by hyperventilation and lowering his pCO_2. Figures 76, 77, and 78 demonstrate this phenomenon. Healthy infants in a cool environment after birth achieve a relatively normal pH in 2 hours although their metabolic acidosis persists.

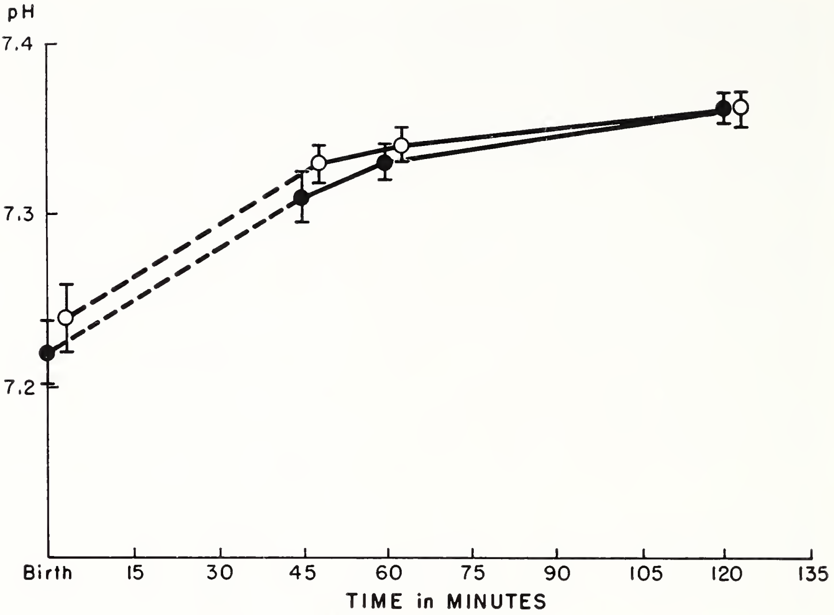

Figure 76.—Mean pH values of 24 infants at two different environmental temperatures during the first 2 hours of life. ○=cool; ●=warm. Vertical bars represents one standard error of the mean. Reprinted, by permission, from Gandy, G. M., et al: Thermal environment and acid-base homeostasis in human infants during the first few hours of life. *J Clin Invest 43: 751–758 (Apr) 1964.*

Silverman. I have also observed the phenomenon of apnea during rapid warming of the skin of cool premature infants by a radiant heat source. It doesn't happen every time but often enough so that we watch for it. When respirations are stimulated by a flick or a loud sound, these small infants resume respirations even though the skin remains warm (36° C. to 37° C.).

Comroe. Another very potent stimulant to respiration is increased body temperature well above normal. Increase in body temperature 3 or 4 degrees above normal can produce hyperpnea violent enough to cause tetany.

Silverman. Thermal hyperpnea is not at all infrequent in premature infant nurseries as the result of accidental overheating of incubators.

Segal. I would like to extend this point. I think that the conference proceedings, so far, could be interpreted by some to suggest that babies should be cooled. The cooling that we have just considered relates only to stimuli which may initiate respiration. I wonder whether there should be some further clarification of some of the broader effects of low ambient temperature.

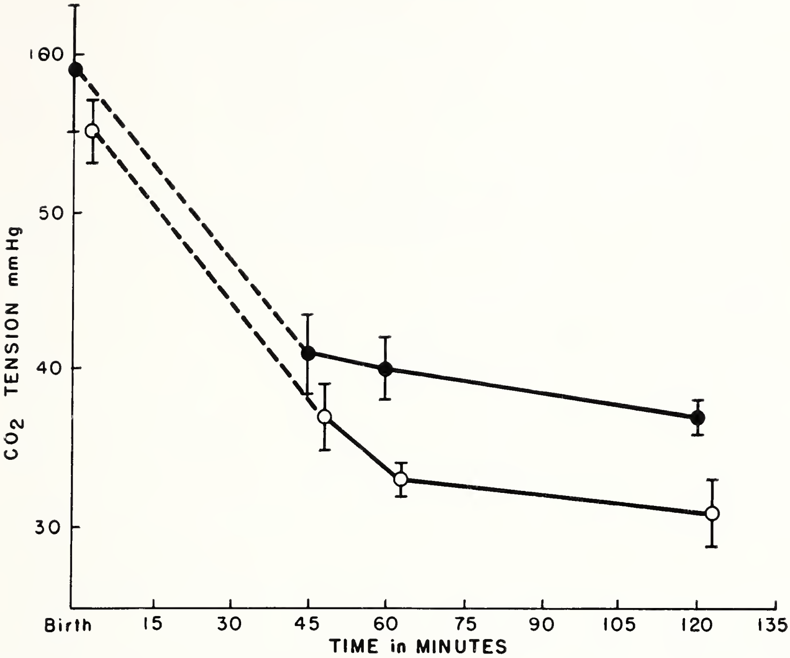

Figure 77.—Mean carbon dioxide tension of 24 infants at two different environmental temperatures during the first 2 hours of life. (Symbols same as figure 76.) Reprinted, by permission, from Gandy, G. M., et al: Thermal environment and acid-base homeostasis in human infants during the first few hours of life. *J Clin Invest 43: 751–758 (Apr) 1964.*

Silverman. We need to be clear about whether it is *temperature* level or *rate of change* that is important in providing stimuli to respiration during cooling or warming.

Cross. One perhaps should think differently about the temperature in relation to resuscitating a baby and nursing a baby. It does seem to me that there are two distinct problems. I think there is a lot to be said for keeping a baby in the nursery reasonably warm—thereby keeping its metabolism down—but if you have a baby who is not breathing, I think there is still the possibility of argument for letting it cool off.

Dawes. If you ventilate a profoundly asphyxiated monkey with 100 percent O_2, giving cardiac massage if the heart does not accelerate within 30 seconds, the blood pressure rises rapidly and O_2 consumption rises to adequate levels within 1 or 2 minutes. Therefore, so far as we know, there is no case for cooling a baby. You cannot reduce the temperature of a baby from 35° C. to 25° C. in 2 minutes.

Comroe. Do you agree or do you object, Dr. Cross?

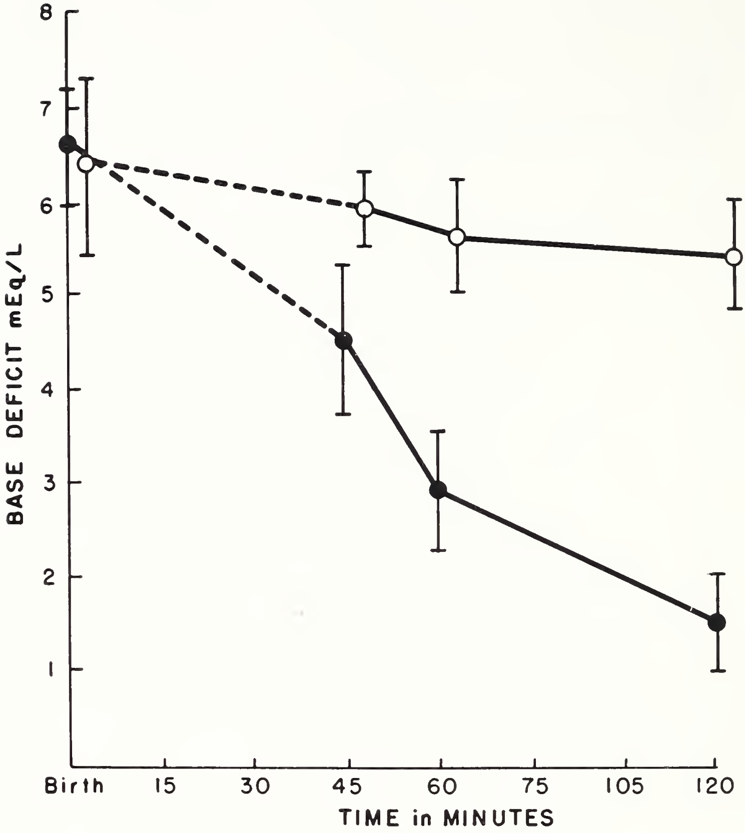

Figure 78.—Mean values for base deficit in 24 infants at two different environmental temperatures during the first 2 hours of life. (Symbols same as figures 76 and 77.) Reprinted, by permission, from Gandy, G. M., et al.: Thermal environment and acid-base homeostasis in human infants during the first few hours of life. *J Clin Invest 43: 751–758 (Apr) 1964.*

Cross. I object.

Dawes. Why?

Cross. I don't object to your facts, but you must realize that occasionally it takes some time to resuscitate a baby.

Dawes. Have you measured their oxygen consumption while doing this?

Cross. No, I wish I had. I wish very much to study asphyxiated infants.

Dawes. But there is no scientific evidence as yet that cooling under these circumstances prevents brain damage or prolongs survival. The published evidence shows that cooling during asphyxia prolongs gasping; it enables the infant to make better use of the available energy. But once you have established artificial respiration and O_2 consumption has risen to normal minimal levels, there should be no need to do more. Until further evidence is produced to show it is advantageous to cool, as well as to oxygenate adequately, I would suggest it is better to concentrate on oxygenation. I am not concerned here with respiratory distress, but only with resuscitation after acute asphyxia.

COMROE. To summarize, people ought to think a little bit more about the mechanism of receptor stimulation. Most, or many, receptors are stimulated by rate of change rather than by the level of excitation, and one ought to investigate the effect of rapid rate of change.

ACID-BASE CHANGES AND RESPIRATION AFTER BIRTH

COMROE. I am going to get back to the first breath. Dr. Karlberg, would you tell us about some studies you have done recently?

KARLBERG. In Stockholm, Drs. L. Engström, G. Rooth, R. Tunell and I [25] have carried out a study* in which we looked for the interrelationships between the onset of respiration and the changes in blood gases and the acid-base balance. The period of investigation was during the first minutes after birth and began as soon as the infant was delivered.

Multiple blood samples were drawn from catheters inserted into one of the umbilical arteries and the umbilical vein. We obtained as many as 10 blood samples within 2 minutes. Oxygen tension (by means of a Clark electrode), carbon dioxide tension, nonrespiratory acid-base balance (base excess), and hydrogen ion concentration (by means of the Astrup microtechnique) were measured. In addition, an initial blood sample from the umbilical vein was subjected to the same measurements. The respiratory movements were recorded as pressure changes in a catheter inserted in the esophagus, a method which was considered to give minimal interference with respiration. In all of the babies, respiration began within 1 minute of delivery.

FREMONT-SMITH. Were these full-term infants?

KARLBERG. Yes, except for one premature of 36 weeks gestation.

Figures 79 and 80 show the values obtained from the umbilical veins plotted against time. This blood must represent the "best" blood which may reach the different chemoreceptors immediately after birth.

The pO_2 varied between 18 and 35 mm Hg. The pCO_2 was around 40 mm Hg with a range of 35 to 45 for most of the infants. This is similar to what Dr. Dawes found in the newborn lambs. Serial samples from the umbilical vein during the first minutes after the delivery (connected dots represent several analyses from the same infant) revealed no significant difference with time. There was no change even after the placenta was delivered.

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*This investigation was supported by grants from the Association for the Aid of Crippled Children, New York, and Expressens Perinatal Research Fund, Stockholm.

The values of base excess revealed a metabolic acidosis with a range of −5 to −10 mEq/liter. The lowered pH was due to a metabolic acidosis, since the pCO_2 was normal.

In order to illustrate the simultaneous changes in the different measurements, the results from the iliac artery are shown in Figure 81. The initial pO_2 varied between 10 and 22 mm Hg, but within the first minutes the iliac

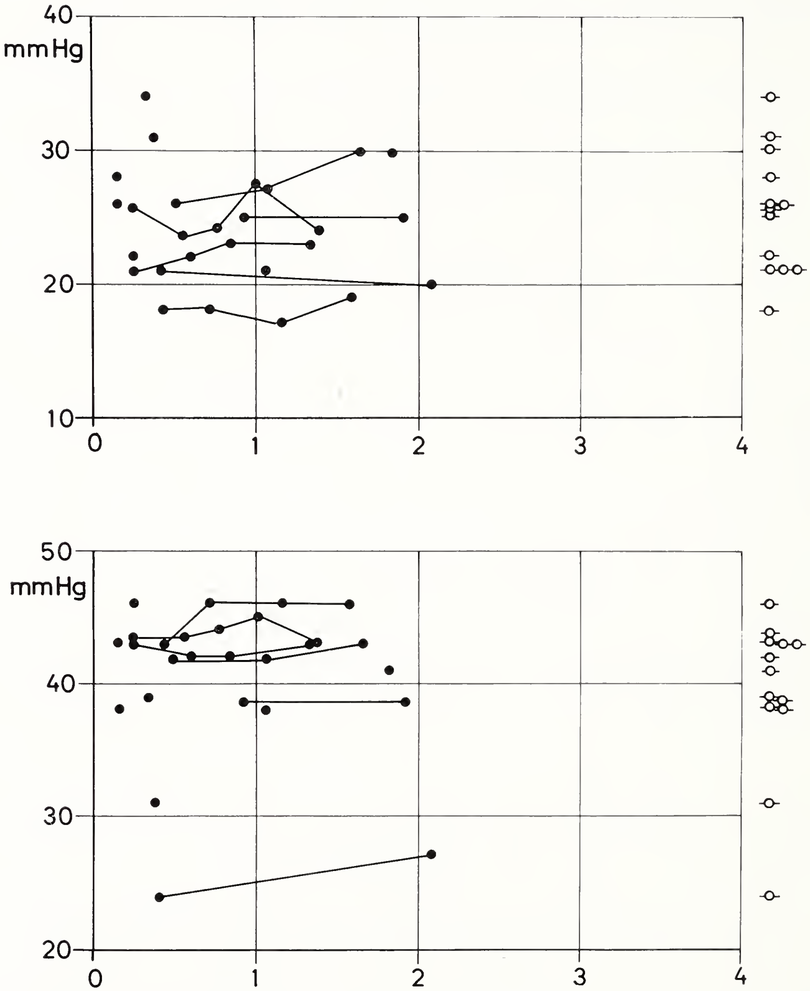

Figure 79.—Oxygen tension and carbon dioxide tension in the umbilical vein blood. Normal cases. To the extreme right in the figures are the initial values plotted without regard to time (*open dots*). Reprinted, by permission, from Engström, L., Karlberg, P., Rooth, G., and Tunell, R: *The Onset of Respiration: A Study of Respiration and Changes in Blood Gases and Acid-Base Balance.* New York, Association for the Aid of Crippled Children (Feb) 1966.

artery pO_2 increased from a level below to a level above that of the umbilical vein.

Although there was a rapid rise, as shown by the family of curves, there was also a wide variation. After 10 minutes, pO_2 ranged from 20 to 60 mm. Only a few infants were studied for as long as 1 hour, but measurements in

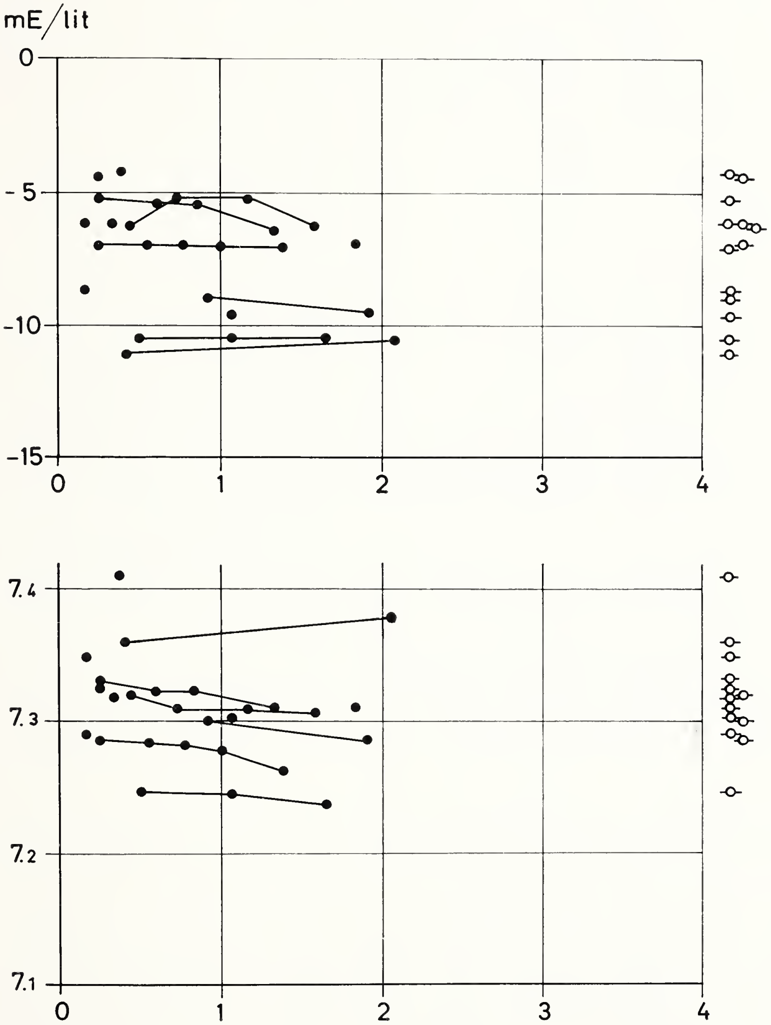

FIGURE 80.—Base excess and hydrogen ion concentration in the umbilical vein blood. Normal cases. To the extreme right in the figures are the initial values plotted without regard to time (*open dots*). Reprinted, by permission, from Engström, L., Karlberg, P., Rooth, G., Tunell, R.: *The Onset of Respiration: A Study of Respiration and Changes in Blood Gases and Acid-Base Balance.* New York, Association for the Aid of Crippled Children (Feb) 1966.

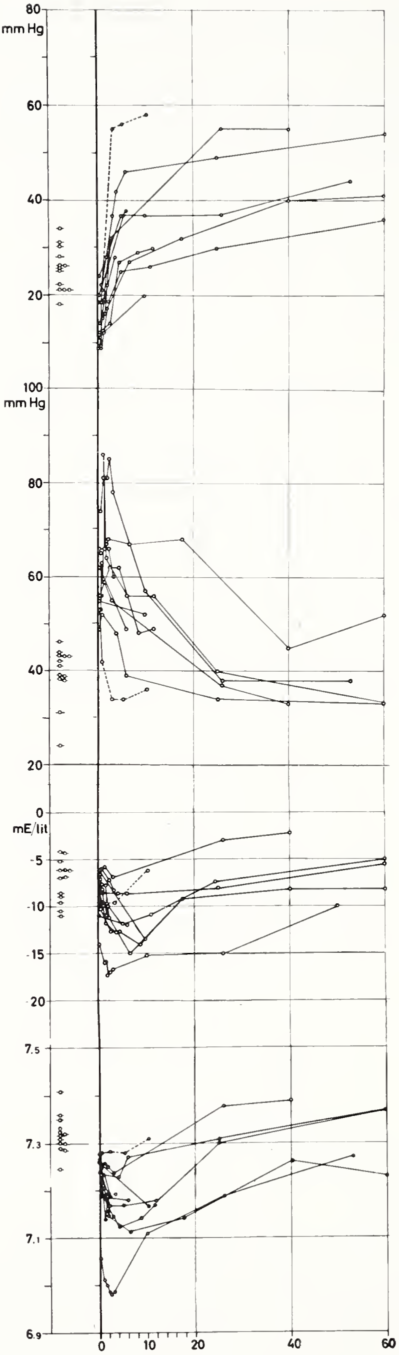

FIGURE 81.—Oxygen tension, carbon dioxide tension, base excess and hydrogen ion concentration in the iliac artery blood. Normal cases. To the extreme left are the corresponding values from the umbilical vein blood as also shown in figures 79 and 80. Reprinted, by permission, from Engström, L., Karlberg, P., Rooth, G., and Tunell, R.: *The Onset of Respiration: A Study of Respiration and Changes in Blood Gases and Acid-Base Balance.* New York, Association for the Aid of Crippled Children (Feb) 1966.

the portal vein indicated that, normally, the iliac artery pO_2 at 1 hour must be above 40 mm Hg.

Oliver. The mean pO_2 in the descending aorta of normal infants at 1 hour of age is 65 mm Hg.[26]

Karlberg. The initial pCO_2, within the first minute, varied between 49 and 72 mm Hg. During the first 2 minutes, the carbon dioxide tension increased by about 15 (1 to 20) mm Hg to 64 to 86 mm Hg followed by a gradual decrease. After 6 to 40 minutes, the pCO_2 of the iliac artery was at the same level as it was initially in the umbilical vein.

Base excess in the iliac artery was between -6 and -14 mEq/liter in the samples taken within the first minute. It fell further (3 to 8 mEq/liter) in the first 2 to 10 minutes, after which the metabolic acidosis gradually diminished.

Because the iliac artery had a high pCO_2 and a low base excess, pH was low. The range was 7.058 to 7.238 in the initial sample taken within the first minutes. With increasing pCO_2 and decreasing base excess, the pH value decreased, and during the first 1 to 6 minutes the individual cases showed pH drops equal to 0.04 to 0.17 pH units. After this time there was a gradual increase in pH, and after 1 hour pH was higher than it was initially.

One of the factors in the normalization of the metabolic acidosis is related to the oxygen available for the metabolism of the tissues. The present study has shown that the oxygen tension in the arterial blood started to increase before base excess changed direction. We have therefore related the oxygen tension at the lowest base excess to the time after birth when the lowest base excess was observed (fig. 82). The turning point of the metabolic acidosis occurs when the oxygen tension has reached a level of about 35 mm Hg (range 20 to 42 mm Hg) independently of the time after birth.

These studies relate the effect of respiration on the blood gases and acid-base balance. Now, let us look upon the interrelated changes from the other side. What effect may the changes in the blood gases and acid-base balance have on respiration?

The study of the respiratory tracings revealed that different types of respiratory patterns could be differentiated. Respiration usually started with a series of single breaths with no clear-cut periodicity. During the first minutes, as well as later, there were periods of crying which generally lasted from one-half to 1 minute. After a transition period of more or less irregular breathing, 13 infants showed regular breathing with a constant rhythm and amplitude. Judging from earlier respiratory studies during the immediate postnatal period with simultaneous volume and pressure recordings, the tidal volumes were estimated to be of medium size. This pattern of respiration will therefore be referred to as "regular medium respiration." The onset of this type of respiration varied from 1 to 10 minutes after birth. In the transitional period some infants showed a periodic regular respiration called "periodic regular medium respiration."

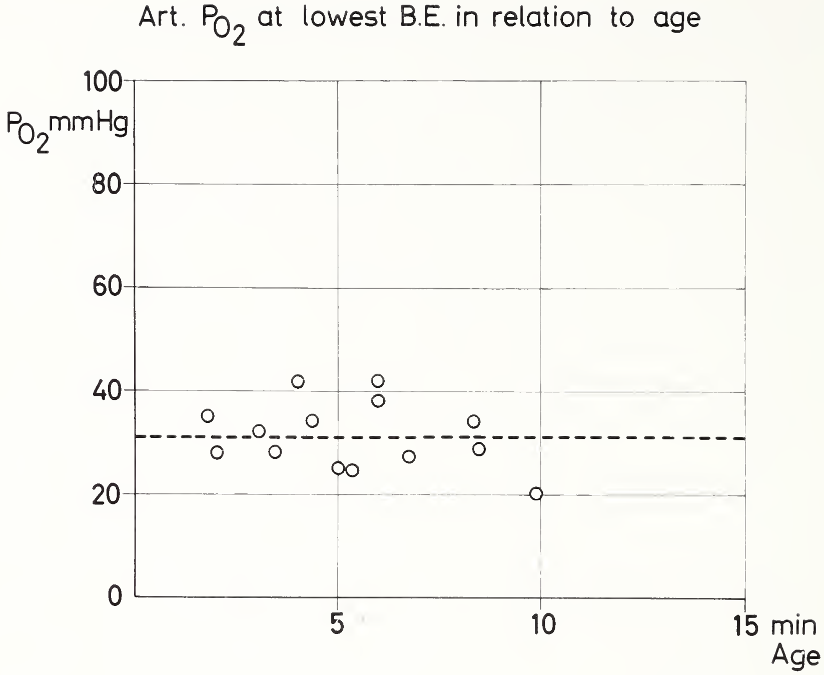

FIGURE 82.—Oxygen tension of the iliac artery blood at which base excess is lowest. The lowest base excess corresponds to the point where it starts to be normalized again after the additional postnatal drop. It will be seen that this happens when pO_2 in the iliac artery blood is about 35 mm Hg regardless of when this happens. Reprinted, by permission, from Engström, L., Karlberg, P., Rooth, G., and Tunell, R.: *The Onset of Respiration: A Study of Respiration and Changes in Blood Gases and Acid-Base Balance.* New York, Association for the Aid of Crippled Children (Feb) 1966.

In most cases the regular medium respiration lasted for several minutes and could only be disturbed by strong stimulation such as suction of the upper respiratory tract. It was not affected by the mere handling of the infant.

When comparing the respiratory data (frequency and pattern) with the changes in blood gases and acid-base balance with time, there is more than a three-dimensional relationship because of the interrelationships between the acid-base parameters. The pH of the blood is the resultant effect of the combined influences of the metabolic component (base excess) and the respiratory component (pCO_2) and the unsaturated hemoglobin.

In order to visualize the relative importance of these three components on the pH in relation to time, the acid-base balance data have been treated in a special way.

The deviation in the respiratory component of the acid-base balance, usually defined as the pCO_2 deviation from 40 mm Hg, has been expressed as the pH change resulting from the pCO_2 deviation.

The deviation in the metabolic component of the acid-base balance, defined as base excess, has been expressed as the pH change resulting from the deviation of base excess at pCO_2 40 mm Hg.

The deviation in pH due to unsaturated hemoglobin has been calculated via its influence on base excess (10 gm of unsaturated hemoglobin binds 3 mEq/liter).

Together with respiratory data, pO_2 and pCO_2, these pH components have been plotted against the time axis (fig. 83). The umbilical vein values were at the ordinary level with a moderate metabolic acidosis (base excess −6.2 mEq/liter). pCO_2 in the first iliac artery sample was high. The onset of breathing was slow. During the first 75 seconds, only seven breaths were recorded. The effect on the blood gases was that pO_2 remains at a very low level, and pCO_2 increased 24 mm Hg. The pH/time diagram shows that at the end of this respiratory period there was a pronounced acidosis which mainly consisted of the respiratory component. The next period of breathing started with vigorous crying for 45 seconds and was then followed by a more irregular but still vigorous breathing until 3 minutes after birth when the regular medium breathing started. The respiratory rate increased gradually to 40 or 50/minute. This respiratory period has been called transitional. Its effect was a rapid decrease in pCO_2 as well as an increase in pO_2.

The metabolic component of the acidosis gradually increased, and the respiratory component decreased. The fact that pCO_2 decreased in spite of increasing metabolic acidosis with decreasing carbon dioxide combining power of the blood further illustrates the capacity of the lungs to eliminate CO_2 at this time of life. Then followed regular medium respiration which was recorded for 5 minutes. pO_2 and pCO_2 remained stable, and there was only a moderate decrease in the metabolic acidosis. No respiratory recordings were obtained during the rest of the first hour. A slow rise of the oxygen tension up to 36 mm Hg and a drop of arterial blood carbon dioxide tension to 33 mm Hg at 1 hour after birth showed that a positive respiratory balance was present during that time. The decreasing pCO_2 could only partly be explained by decreasing metabolic acidosis.

Figure 84 shows the findings in an immature infant who had signs of idiopathic respiratory distress syndrome during the first hours of life. This infant had a low pO_2 which was only increased by oxygen administration, a progressively increasing base excess and a pCO_2 which was high initially, then lowered somewhat only to become elevated again at 60 minutes.

Now, what can be said from these studies about the onset and regulation of breathing in a newborn infant? According to Burns,[27] the central control of respiration seems to be elicited by spontaneous discharging groups of cells in the brain stem. The activity of this respiratory center is influenced by two main types of stimuli: (1) nonrespiratory neuronal activity, and (2) respiratory reflexes and humoral stimuli.

At the moment of birth, the net sum of nonrespiratory neuronal activity input must be increased suddenly. Due to the hypoxia, hypercapnia, and metabolic acidosis at birth, the humoral stimuli might be expected to give

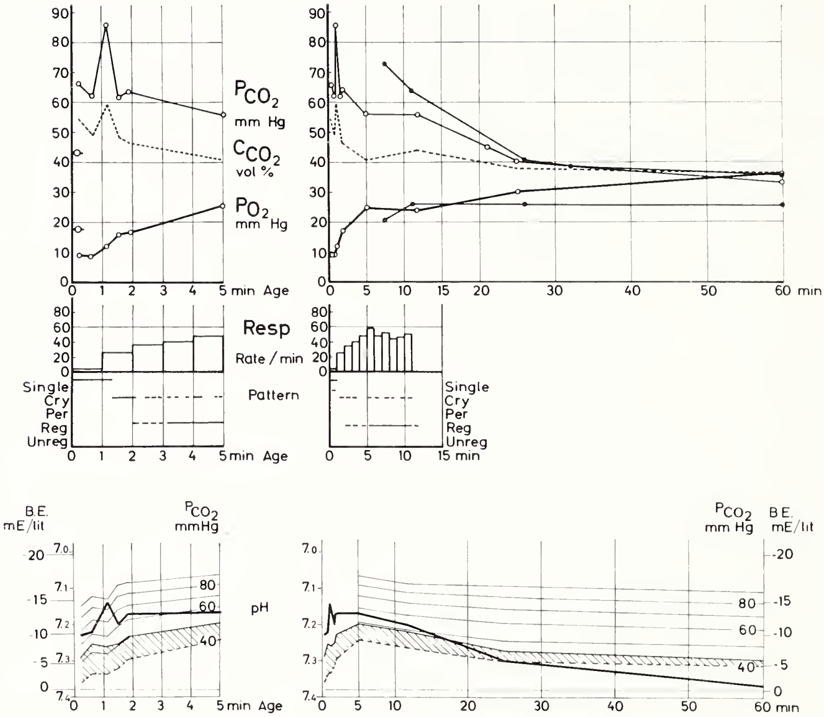

FIGURE 83.—Relationship between establishment of respiration (respiratory patterns and rate), oxygen tension, total carbon dioxide content, and dioxide tension. Normal infant. Open circles=iliac artery blood. Big open circles=umbilical vein blood. Filled circles=portal vein blood. Dotted line=total carbon dioxide content. Histogram=respiratory rate. Pattern=respiratory pattern. Arterial blood pH/time diagram. Thick line gives pH on left-hand scale and pCO_2 on right-hand scale from the isobars. Area (*white+shades*) between thick line for pH and dotted line represents pH deviation due to pCO_2 (respiratory acidosis). Area (*shaded+lower white*) under line represents pH deviation due to base excess (metabolic acidosis). Shaded area represents pH increase due to unsaturated hemoglobin. In the left part of the figures, time scale is enlarged during the first 5 minutes. Reprinted, by permission, from Engström, L., Karlberg, P., Rooth, G., and Tunell, R.: *The Onset of Respiration: A Study of Respiration and Changes in Blood Gases and Acid-Base Balance.* New York, Association for the Aid of Crippled Children (Feb) 1966.

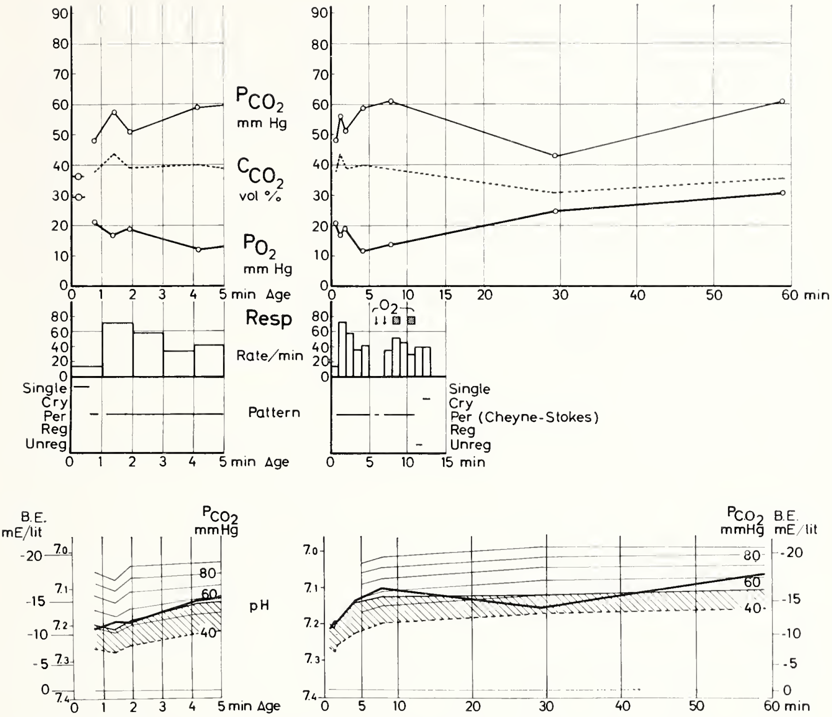

Figure 84.—Relationship between establishment of respiration (respiratory patterns and rate), oxygen tension, total carbon dioxide content, and dioxide tension. Immature infant with developing idiopathic respiratory distress syndrome. (For symbols, see fig. 83.) Reprinted, by permission, from Engström, L., Karlberg, P., Rooth, G., and Tunell, R.: *The Onset of Respiration: A Study of Respiration and Changes in Blood Gases and Acid-Base Balance.* New York, Association for the Aid of Crippled Children (Feb) 1966.

an intense stimulation of the respiratory centers. Therefore, one would expect an immediate and forceful onset of breathing at birth. The respiratory recordings, however, show that this is not the case. Instead, the first minute is characterized by single irregular breaths followed by a period of transitional irregular breathing. Regular medium breathing begins only after several minutes. Thus, it seems probable that there exists some inhibitory factor at birth which acts on the respiratory centers.

A probable inhibitory factor seems to be hypoxia. Breathing is initiated by the intensive nonrespiratory stimuli and the increasing carbon dioxide and metabolic stimulation of the respiratory center. The results indicate that in this hypoxic state a certain degree of hypercapnia and/or metabolic acidosis has to develop before regular breathing begins. In most cases, this happened at a pH of 7.20 to 7.15. As pO_2 increases, the sensitivity of the center improves, and regular respiration is continued even with decreased humoral stimuli.

Comroe. Is it possible, in a newborn infant who is breathing, to hyperventilate the infant mechanically with oxygen so as to diminish the chemical stimulus to breathe? Has this been done? If so, is there a depression of breathing or apnea?

I am asking this because of the work done by Haldane many years ago. We all came to the conclusion that if, by hyperventilation, we lowered the pCO_2 of an adult man to a certain level (somewhere in the 20's), apnea occurred when the hyperventilation was stopped. We now know that this is not true, and Haldane and his subject apparently knew too much respiratory physiology and what to expect on the basis of theory. When Fink [28] repeated this with a group of individuals who knew nothing about respiratory physiology—and they were selected because they were all anesthesiologists, which I think is a commentary on the profession—it was found that they could hyperventilate or be hyperventilated mechanically until the alveolar pCO_2 decreased to as low as 16 mm Hg; when the period of hyperventilation stopped, they breathed almost normally. When these same individuals were lightly anesthetized and then hyperventilated, they *did* develop apnea at the end of the hyperventilation.

I think that we might get some information as to what is running the respiratory mechanism, if, after the breathing starts in the newborn, we are able to eliminate or reduce the *chemical* stimulus and see what is left—whether the awake newborn baby behaves similarly to the awake adult.

Karlberg. As far as I know, this has not been done, but I think it is possible to do it in newborn infants.

Comroe. Dr. Dawes, when I asked you earlier to introduce this by talking about the first breath, you said there were really no problems with the first breath. It was the second breath that bothered you.

Dawes. Right.

Comroe. What did you mean by that? You seem pretty well convinced that you know what initiates breathing.

Dawes. Yes. In animals delivered by cesarean section, the tying of the cord and consequent asphyxia starts the breathing. In animals, or in babies delivered naturally, other sensory stimuli may be important. Babies may be delivered in good condition and cry as soon as their face emerges. They have certainly been compressed in the vaginal canal.

Comroe. You said that in the infant delivered by cesarean section it is asphyxia, and in lambs it is asphyxia. What is the mechanism by which respiration is stimulated by asphyxia?

Dawes. I have presumed that this is through the systemic arterial chemoreceptors, but so far as I know, no denervation experiments have been carried out. I think that the respiratory reflexes are functional at birth, though we do not know for certain when they first become functional.

COMROE. I think I can give a little evidence on this, not from my own work but from that of Dr. Michael Purves [29] who was working with us last year and Dr. June Brady [30] who is working with us now. They have studied the response of both the newborn lamb and the newborn infant to a high and low oxygen inhalation. In both species, inhalation of O_2, presumably by inactivation of carotid and aortic bodies, leads to temporary depression of breathing. This indicates that O_2 chemoreceptors are active as soon after birth as studies can be done.

Dr. Purves has also given newborn lambs high oxygen to breathe and found an instantaneous depression of breathing. He then blocked the carotid bodies and repeated the inhalation, and there was no depression. He is pretty well convinced that this is a reflex arising in the carotid bodies.

DAWES. Yes. If you inject cyanide into a newborn rabbit, you get hyperpnea, which is abolished by denervation of the carotid bodies only.

COMROE. I believe that Dr. Cross also reported action potentials from the carotid body. Is that correct?

CROSS. Yes. I don't think Dr. Dawes accepts it, but I do.

DAWES. I do accept your evidence. Your experiments were done on mature lambs. One would like to know how young they were.

CROSS. Thirty days.

COMROE. In a baby born at 7, 8, or 9 months, are these various reflexes effective? If not, is the immaturity at the sensory receptor, centrally, or on the motor side?

DAWES. We would also like to know how changes in arterial pO_2 and pCO_2 interact on the total ventilation of the newborn baby.

COMROE. I can give you a little information on that. Again, Dr. Brady has been doing this on a few newborn babies, and her data so far indicate that their response to a combination of low oxygen and high CO_2 mixtures is very much like that of the adult.

DAWES. This is a very interesting question. One would like to know how the thresholds and sensitivities of these sensory receptors are determined *in utero*. One can guess how the reaction to pCO_2 is determined, because the pCO_2 of the fetus is not very different from that of the mother. But the arterial pO_2 is quite different in the fetus and newborn. Does the sensitivity of the receptors change after birth?

COMROE. Do you believe that the chemoreceptor cells are activated by low oxygen but that the impulses which go to the respiratory center are ineffective or not maximally effective until something else happens?

DAWES. This is possible. I would like to see a single fiber analysis of chemoreceptor action potentials in the fetus at various gestational stages, if this is possible.

COMROE. Dr. Dawes says we don't know at what age in the fetus the various reflexes develop and become active. It may well be that those that cause apnea develop long before those that excite the respiratory center.

Interestingly enough, there are a number of reflexes which are known to cause apnea. These include the submersion reflex, the thoracic chemoreflexes (von Bezold-Jarisch reflexes), carotid sinus stimulation, upper respiratory tract irritation from chemicals, and swallowing. Most of these are hard to demonstrate in an unanesthetized man, and so the various things which cause apnea in animals, and which may be operative in the fetus at a certain stage, may pass out of the picture later on and all we see are those that stimulate. It is difficult to produce reflex apnea in an adult human being but easy in certain animals.

I think it is also possible that reflexes involving respiration may involve the whole animal, because we know that reflexes that excite the carotid bodies can produce convulsions, so that impulses destined primarily for the respiratory center can spread to the whole brain and produce widespread motor activity. I think it is also known that it can work the other way round, that is, that ventilation with oxygen can remove this increased cerebral activity in anoxic patients; it puts them to sleep or at least allows them to sleep.

Karlberg. Dr. Comroe, may I stick my neck far out? We have been speculating on the role of low level pO_2. We know it is very low when the baby is born. If this level is representative of conditions before delivery and labor, it may suppress the respiratory center, and the pCO_2 level of around 40, which is kept stable by gas transfer across the placenta, will not stimulate respiratory movements.

Immediately after delivery, conditions change rapidly but with great variation. May I give some examples of possible different types?

During spontaneous deliveries with complications causing an impaired fetal gas exchange, the fetus will develop a considerable metabolic acidosis as well as a respiratory one. In spite of a low pO_2, the biochemical stimuli will be great enough so that the baby starts to breathe regularly immediately after birth. Clinically, we may consider this baby very vigorous, but he may have difficulties because of the metabolic acidosis.

In babies with severe hypoxia, hypercapnia, and metabolic acidosis, the biochemical atmosphere is too abnormal for the initiation of breathing and will only become worse as apnea progresses. The course has to be altered by resuscitation.

Avery. I would like to suggest yet another way of looking at this business of inhibition *in utero,* and rhythmicity thereafter, in terms of rates of changes of blood gases. I can conceive that gas exchange probably is going on moderately continuously in the placenta, but the lung has to cycle air in and out, and there have to be changes in pO_2 and changes in pCO_2 in arterial blood. Therefore, the first derivative of the pCO_2 or the pO_2 may, in fact, influence the level of ventilation.

There is some experimental evidence consistent with this idea. This was first suggested by Yamamoto[31] and Grodins,[32] but studies by Dutton and others,[33] oscillating inspired mixtures of CO_2 in animals, suggest that the larger the oscillation, the greater the ventilation. It would be interesting to measure the fluctuations in blood gases in the fetus and compare them to the air-breathing newborn infant.

CROSS. There is one point about Dr. Karlberg's work which I think is important. If the ductus is wide open, the pO_2 going to the brain may be quite different from the pO_2 in the iliac artery.

KARLBERG. It is quite clear, as Dr. Cross has pointed out, that the circulatory adaptation occurring simultaneously with respiratory adaptation is of importance. In some infants, we have pushed the catheter *farther* up in order to obtain samples above as well as below the ductus arteriosus after 10 or so minutes of age. There were differences, but the changes during the first minutes were greater than these differences. Therefore, we believe that the reported pattern of changes is significant, although the various levels may vary with the place in the circulation.

There is another possibility which may have bearing on the initiation of breathing. Before the first breath, or any effective first breaths, the fetal type of circulation may persist with transfer of blood from the placenta through the ductus venosus—foramen ovale—left side of the heart to the upper part of the baby. The respiratory center will be supplied with placental blood, which we have found to be stable.

JAMES. If you obtained a left atrial sample rather than one from the aorta, I think you probably would get much higher pO_2. We did saturations and pH's upon left atrial and aortic samples from 2 minutes after birth. There is a great difference in the calculated pO_2 between the two sites.

OLIVER. We have observed the same thing with the direct measurement of pO_2.[26]

COMROE. I think the question which Dr. Dawes raised should be brought into the open.

The aortic bodies, in general, are in the region between the aortic arch and the pulmonary artery. In the adult of all species that I know of, the aortic body chemoreceptors receive their blood supply from a small branch of the aortic arch or of the coronary artery, and their arterial blood comes entirely from the systemic circulation. In the adult cat, the blood supply comes from a branch of the coronary artery. But in the fetus of the cat and the human being, there is an additional branch from the pulmonary trunk which supplies these chemoreceptor cells (fig. 85).

In the fetus, then, there is a possibility that these cells get their blood from the pulmonary artery. Shortly after birth, this pulmonary artery branch closes off completely, and the aortic bodies then get their blood from

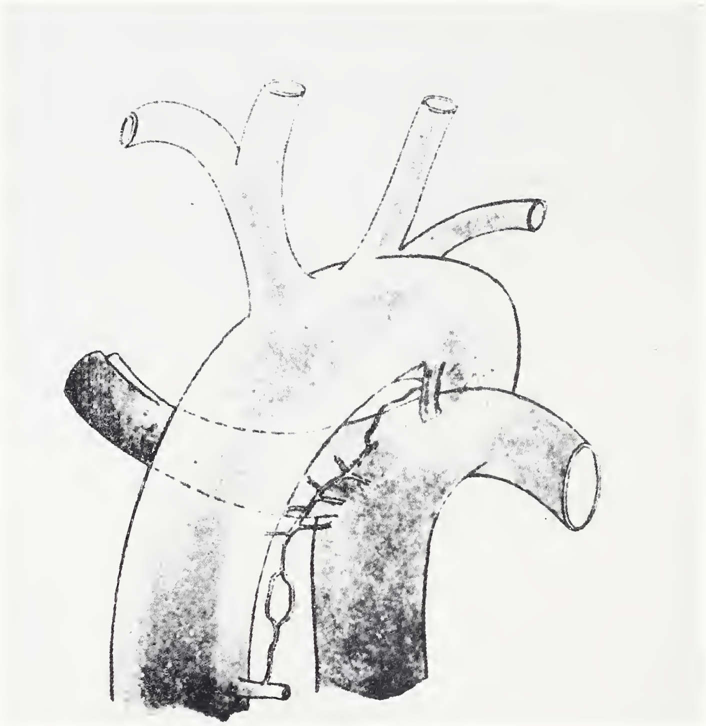

Figure 85.—Artery to the aortic bodies in the adult cat. A patent vessel arises from the left coronary artery and runs to the chemoreceptor tissue (not shown) between the ascending aorta and pulmonary trunk. It continues as a closed cord to the bifurcation of the pulmonary trunk; this portion is usually patent in the fetus. Reprinted, by permission, from Goormaghtigh, N., and Pannier, R.: Les paraganglions du coeur et des zones vaso-sensibles carotidienne et cardio-aortique chez le Chat adulte. *Arch Biol (Liege) 50: 455–533, 1939.*

the aorta through the branch of the coronary artery or of the aortic arch, and they are then getting systemic arterial blood.

Very recently, Dr. Helen Duke[34] published a paper with a schema showing an artery coming off the pulmonary trunk of an adult cat with a big pulmonary body situated on that artery. Since I had never been able to find a pulmonary body in the adult cat or dog supplied by a pulmonary artery or even a branch, I asked a graduate student, Mr. Amrit Lall, to tie off the pulmonary trunk centrally and the right and left pulmonary arteries distally so as to form a closed segment. He pumped saline into this segment to a pressure of about 25 mm Hg and measured the pressure over a period of time. It remained constant for 30 minutes or more, so that there could not be any small arterial exits. In addition, he was unable to find any branch of the pulmonary artery in the adult cat by using injection techniques. However, there is a pulmonary artery branch in the fetus. Essentially then, there is a second ductus, a very small one, which supplies chemoreceptor tissue.

DAWES. In the fetus with a moderate degree of asphyxia and a high pulmonary arterial pressure, you may get preferential flow from the pulmonary artery, rather than the aorta, to the aortic chemoreceptors.

COMROE. Why do you think that this particular group of chemoreceptor cells has a dual blood supply? Is it so it can get blood from either system in the fetus but only from the aorta in the adult?

DAWES. It may be an accident of development, as the major arterial branches originate from the branchial arch system.

JAMES. In the newborn monkey, asphyxiated beyond the point of the last gasp and then resuscitated, the subsequent recommencing of gasping occurs some time after the blood is fully saturated with oxygen and with arterial pCO_2 values as low as 15 mm Hg.

COMROE. You haven't turned a fan on them?

JAMES. No, we have not. The body temperatures, however, fall throughout this period of time. The animals are still very acidotic. Their pH at this time is between 6.9 and 7.0 because of the persistence of severe metabolic acidosis. Gasping will then continue for several minutes, depending upon how long the duration of asphyxia has been, and is subsequently followed by rhythmical breathing. After severe asphyxiation, the duration of time before the establishment of rhythmical breathing is about twice as long as the time to initiate it.

COMROE. This is quite interesting because there are many who believe that all the effects of CO_2 on peripheral or central chemoreceptors are due to an increase in the hydrogen ion concentration.

KLAUS. Dr. Dawes, when you clamp the cord and the lamb jumps off the table, what makes him wake up and start to breathe? What happens in his brain?

DAWES. There are said to be electroencephalographic changes.

FREMONT-SMITH. An orienting reflex, perhaps, is taking place.

COMROE. The main trouble is that the brain is a rather complicated organ, and one really wants to know something about what is going on in the reticular activating system as well as what is going on in the motor and sensory cortex and other parts of the brain.

ALDRICH. Wouldn't the point that Dr. Klaus brought up be important—that one of the things we probably ought to know more about is the relationship of cortex, as well as the subcortical areas, to the activation brought about by the chemoreceptors?

COMROE. I have a feeling it is a very important question, because the unrefuted evidence so far is that the adult respiratory center can maintain respiratory rhythmicity all by itself.

Dr. Dawes, will you give us a little background on the changes that occur in the cardiovascular system during the transitional period and why they occur, as you see the evidence at present?

THE PULMONARY CIRCULATION

Dawes. These experiments were done in collaboration with Joan Mott, Ben Ross, Sid Cassin, and Leonard Strang[35] on anesthetized fetal lambs.

The pulmonary vascular bed in the fetus is intensely reactive.[36] Temporary occlusion of the left pulmonary artery, to produce transient ischemia, causes a subsequent reactive hyperemia during which flow may rise to 100 ml/min or more in a lamb of 3 kg at term. Similarly, injection of histamine or acetylcholine causes extreme vasodilatation.

In many lambs, we have seen periods of spontaneous vasodilatation during which left pulmonary arterial flow has increased to as much as 60 ml/kg/min with no change in arterial pO_2 or pCO_2. If flow through the right lung changed in the same proportion, total pulmonary flow would approach 150 ml/kg/min, which is almost as much as umbilical blood flow. Therefore, we need no longer think of pulmonary blood flow as being low, under all circumstances, in the fetus.

Left pulmonary arterial pressure-flow curves were measured. The left pulmonary artery was joined to the left carotid via an electromagnetic flowmeter, and a vertical tube was attached to this circuit. From time to time, the vertical tube was filled with blood, the carotid was occluded, and blood was allowed to flow into the pulmonary artery from the vertical tube while pressure was recorded on the X-axis and flow on the Y-axis of an X–Y recorder. The changes in left atrial pressure were insignificant. After obtaining observations in the fetal condition, the lungs were ventilated with different gas mixtures.

Rhythmic ventilation of the fetal lungs with indifferent gas mixtures (0–3% O_2 with 7% CO_2 in N_2) caused little or no change in arterial pO_2 or pCO_2 (fig. 86). When the mixtures were replaced with N_2, there was further vasodilatation, and with air, still further vasodilatation.

From these results, the pulmonary vascular conductance, that is, the slope of the pressure-flow regression line, has been calculated per kilogram of body weight. In the *fetal* condition we have:

$$\text{Conductance/kg} = 1.82 + 0.065\ pO_2 - 0.057\ pCO_2.$$

The regression constants are significantly different from zero, hence both arterial pO_2 and pCO_2 affect the conductance of the unventilated fetal lung independently. The equation states that you obtain about the same degree of vasodilatation on raising pO_2 or lowering pCO_2 by 1 mm Hg each. At birth, there is a greater rise in arterial pO_2 than there is fall in pCO_2, so

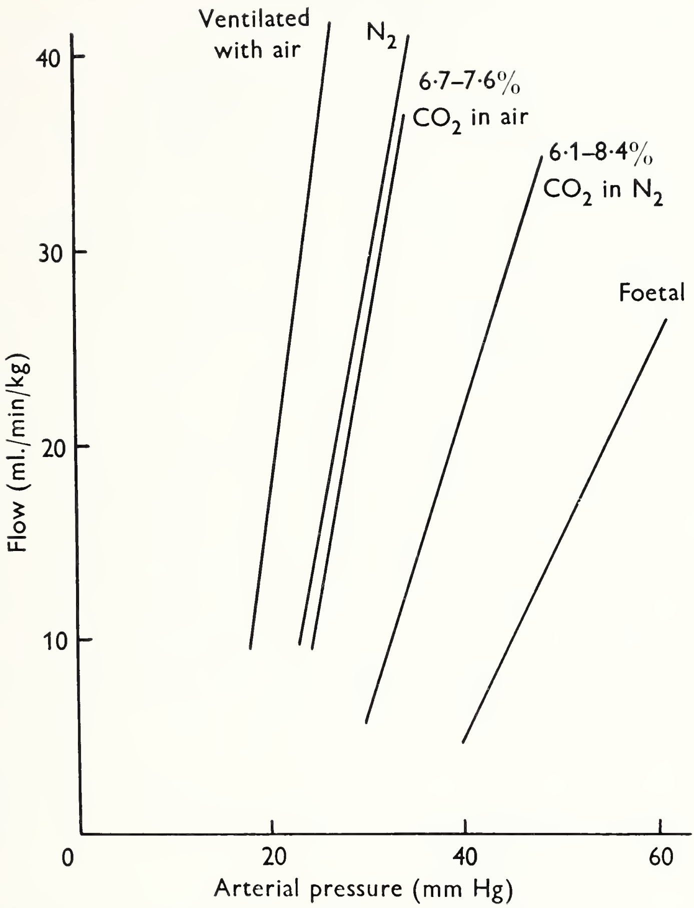

FIGURE 86.—Mean left pulmonary pressure-flow diagrams for seven lambs in the unventilated fetal condition and after ventilation with different gas mixtures. Reprinted, by permission, from Cassin, S., et al: The vascular resistance of the foetal and newly ventilated lung of the lamb. *J Physiol (London) 171: 61–79 (May) 1964.*

one might suppose the changes in pO_2 to be more important so far as pulmonary vascular conductance is concerned. In *ventilated* lungs the following equation was obtained:

$$\text{Conductance/kg} = 2.42 + 0.065\ pO_2 - 0.057\ pCO_2.$$

The difference in the residual constant from 1.82 in the fetal lung to 2.42 in the ventilated lung gives a measure of the change in vascular conductance irrespective of changes in blood gas tensions. The regression constants for pO_2 and for pCO_2 are the same in the two equations.

All these lambs were still attached to their mothers with continuing umbilical flow. Had there been a *direct* effect of the gas tensions on the pulmonary vessels when the lungs were ventilated, one would have expected that the regression constants for pO_2 and pCO_2 would alter. The fact that they did not alter suggests the possibility that the principal means by which the vascular resistance of the lung is controlled, in the newborn as in the fetus, is by the arterial pO_2 and pCO_2 and not by a direct action within the lung itself. This is an important question to resolve when considering both respiratory distress and resuscitation of the newborn.

Finally, even in premature lambs at 90 days gestation age or less, when the lungs cannot yet be expanded, a brief period of asphyxia causes intense pulmonary vasoconstriction, as it does in mature fetal lambs.

COOK. What are the limits for the usefulness of this equation? It appears that if you had very asphyxiated animals, you would have a negative conductance. It is interesting that according to this equation, the pO_2 may decrease to zero without reducing the vascular conductance to zero, but a rise in pCO_2 to around 70 would result in a zero conductance.

DAWES. These equations should be considered only in the context of the experiments which were done. I should have explained that the arterial pO_2 only ranged between about 15 to 45 mm Hg and the pCO_2 from 25 to 50 mm Hg. We did not want to range too widely at first. So far as we can see from the present data, the results for pO_2 and pCO_2 are additive, but we cannot extrapolate beyond our range. We hope to extend the range of values in future experiments.

COOK. Dr. Leonard Strang,[37] working with newborn lambs, showed a very rapid response in pulmonary vascular resistance with changes in the composition of inhaled gas.

COMROE. Later or earlier work?

COOK. Earlier. At the time we were impressed that the responses were more rapid (15 to 20 seconds) than could have been explained by a change in the gas content of the blood going to the lung.

DAWES. Yes, we started off that season's work with your observations and those of Joan Mott and myself in mind. We were delighted to find we were both right. Ventilation with an indifferent gas mixture (e.g., 3% O_2 in 7% CO_2) caused vasodilatation, as did reducing the CO_2 content of the inspired gas. We did not deliberately set out to study the mechanisms. I agree that changing the gas mixture does have a rapid effect, but I am reluctant to guess at the mechanism. It is going to take a lot of investigation.

COMROE. What are the implications of therapeutic importance?

DAWES. So far as the etiology of respiratory distress is concerned, one may suppose that asphyxia causes vasoconstriction in the lung. Then, not only will the lung receive blood which contains little O_2 but also little blood. The lung may become worse off than the heart and brain, to which the blood supply is maintained. As a result, there may be asphyxial disorganization of the cells within the lungs.

COMROE. What is the lowest pulmonary blood flow you have seen in relation to total blood flow?

DAWES. We have seen left pulmonary arterial blood flows of less than 10 ml/min in lambs weighing 4 kg. This is an extreme degree of vasoconstriction.

SMITH. Experimentally?

DAWES. Yes, as a result of asphyxia. One of the difficulties in giving figures about this is that I suspect our operative procedures do interfere with the normal conditions. We have changed the operative procedures greatly since the experiments that were reported in 1953 and 1954. We use much less anesthetic, we open the chest less widely, and I think that the actual dissection is done more rapidly, and I hope we are causing less disturbance. Certainly, we are getting much higher steady resting pulmonary blood flows than we did formerly.

STAHLMAN. We have measured the effect of hypoxia on the measurement of pulmonary blood volume in a different way, by measuring the changes in mean transit time across the lung in the intact normal newborn lamb. Catheters are positioned in the pulmonary artery and in the left atrium as injection sites, and in the aorta as a withdrawal site. Injection first into the pulmonary artery, with the pullout from the aorta, and then into the left atrium, with the pullout from the aorta, each gives a volume of blood between these two sites in time. The difference between these two volumes, presumably, is the volume across the lung.

Measurements while breathing room air are then repeated with the lamb breathing 7.5 percent oxygen, and the change in these differential mean transit time volumes is calculated. A fall in pulmonary blood volume of as much as 30 percent has been seen during lower O_2 breathing.

COMROE. I am not quite sure what volume of blood in the pulmonary circulation you are particularly interested in. The capillary volume is a small fraction of the total pulmonary blood volume.

STAHLMAN. This will include all the blood between the pulmonary artery and the left atrium and not just the pulmonary capillary blood flow.

COMROE. But do you know whether the changes are in the pulmonary venous blood volume, the venular blood volume, the capillary, or the arterial blood volume?

STAHLMAN. If one measures the slope volume following pulmonary arterial injection, which presumably excludes the larger blood vessels in the lung, when breathing room air and low oxygen, it is considerably less during hypoxia.

JAMES. Dr. Comroe, do you think that vascular fluid shifts under these circumstances are the same as they are in the adult?

COMROE. Based on Starling's hypothesis, and considering all the tissues to be healthy and normal, this would depend upon the colloidal osmotic pressure and the pulmonary capillary (transmural) pressure. I don't know what the colloidal osmotic pressure is, or what the capillary pressure is under these conditions of extremes of high and low pressures.

When there is relaxation of the pulmonary arterioles, is there much increase in pulmonary capillary pressure? There isn't in the adult with a patent ductus arteriosus who then has a large additional flow into his pulmonary artery. It just goes into a sink, and the pulmonary capillary pressure doesn't necessarily rise because of the increased flow.

JAMES. I wouldn't think it would in the fetus, either.

RUDOLPH. In many situations in the adult animal, the pulmonary flow can be increased considerably without affecting left atrial and pulmonary venous pressure. This, of course, depends on left ventricular function. In the newborn calf in which an artificial shunt has been introduced between the aorta and pulmonary artery, pulmonary blood flow may be increased by opening the shunt. Under these circumstances, increased pulmonary blood flow does result in an increase of left atrial pressure.

I would like to bring up one question regarding the sites of action of the oxygen and the CO_2 changes. There is some evidence in the newborn animal, specifically in the calf, that the site of effect of oxygen, at least, occurs locally on the pulmonary vessels and not through the aortic and carotid chemoreceptors. This evidence is provided by Vogel[38] who demonstrated in perfused calf lungs that where the pulmonary and systemic circulations were separately perfused, pulmonary vascular resistance could be increased if the pO_2 in blood perfusing the pulmonary circulation was depressed. A decrease of systemic pO_2, however, had no effect on pulmonary vessels.

DAWES. Some years ago, we did experiments on isolated perfused fetal lambs' lungs.[39] On ventilation with N_2, there was vasodilatation. On changing to ventilation with air, there was further vasodilatation. We concluded that there was a local effect, but this is not inconsistent with the present results. The fact that a local effect can be demonstrated in isolated lungs does not necessarily mean it is of overriding importance *in vivo*. We are dealing with a very complex system in which it is possible that there may be both a local effect and one on systemic (and, if they are functional, pulmonary) arterial chemoreceptors.

CLEMENTS. May I add a further thought, since I think it bears directly on where we are going? I think I am correct in saying that at this moment we have very sparse information on the relationship between pulmonary perfusion and the metabolic requirements of the tissue, both in the fetal and in the adult state. One very important area of future research is to determine what the minimal perfusion is over a long-term basis, consistent with health of the alveolar tissues, or on a more acute basis, what this minimum perfusion level might be.

Dawes. I quite agree.

Comroe. We have made observations dealing with a possible mechanism of pulmonary vasoconstriction (fig. 87). Ordinarily, when one injects a stimulant material at the beginning of the aortic arch, it first reaches the aortic body and a fraction of a second later it reaches the carotid body, so that the effects of stimulating the two bodies are mixed—the effects of aortic and carotid body stimulation are added or subtracted.

On the basis of work of the past 30 years, it has been assumed that the effects of carotid body stimulation are identical with those of aortic body stimulation. Therefore, practically all research on these chemoreceptors has been done on the carotid body.

We devised a simple method to separate, in time, the aortic body and carotid bodies by placing a coil of plastic tubing in each common carotid artery in the neck. If a stimulant is injected at the beginning of the aortic arch, it will affect the aortic body at once but will not reach the carotid bodies until 30 to 60 seconds later, depending upon the size of the coils and the animal's cardiac output. Unless the injected material is inactivated in the bloodstream between the time it reaches the aortic and carotid bodies, the concentration in the aorta would be about the same as the concentration in the carotid blood, because the aortic flow is turbulent flow and the chemical mixes with blood at once.

Figure 88 shows that when a drug (nicotine) which can stimulate both the carotid and aortic bodies is injected into the arch of the aorta, it almost instantly produces an aortic body response and much later a carotid body response (after the alveolar and arterial pO_2 and pCO_2 have returned to normal). In the dog, the respiratory response from the aortic body characteristically is small, and that from the carotid body is large. This is a *quantitative* difference. The cardiovascular effects, however, differ *qualitatively*. The carotid body response is mainly bradycardia. The aortic body response is almost always tachycardia and hypertension.

Figure 89 shows again a brief hyperpnea of aortic body origin followed by a greater hyperpnea of carotid body origin. Again, there is tachycardia and hypertension of aortic body origin followed by hypotension and bradycardia. The heart actually stops for 5 or 10 seconds.

In recent experiments by Stern, Ferguson, and Rapaport in our institute, another qualitative difference was found in the dog. Carotid body stimulation by nicotine did not produce pulmonary vasoconstriction, but aortic body stimulation (also by nicotine) produced definite pulmonary vasoconstriction.

In summary, both carotid and aortic bodies affect respiration in the same direction, but, with one exception, they affect the cardiovascular system differently—both produce vasoconstriction in the limbs. This separation of the two sets of chemoreceptors should be easy to do in the adult of any species, although I don't know how the method would work in the fetal circulation if there is a vessel to the aortic body from both the aorta and the pulmonary artery.

AVERY. I would like Dr. Dawes to go back to the question I asked him earlier. What is the bronchial blood flow to the fetus, and how much can you infer about changes in terms of the lung's overall nutrition from what you measure in the pulmonary artery?

DAWES. We don't know. I can only speculate that the flow is low. There are no measurements. I think it is highly desirable that there should be, but I know of no evidence bearing on this. Perhaps you have some, Dr. Comroe.

COMROE. No, I haven't.

POTTER. When one has a fetus dying of anoxia, extreme distension of the capillary bed of the lung is, presumably, one of the characteristic findings. Does the extent or degree of anoxia make a difference in the extent of constriction? Do you think, Dr. Dawes, that the early or temporary effects might be constriction, with a subsequent dilatation, the latter having a more detrimental effect on the circulation?

DAWES. With acute asphyxia of 3 minutes or more, there is strong pulmonary vasoconstriction. If asphyxia is prolonged even further, the blood pressure begins to fall and pulmonary flow will then be even less. I don't know whether there is terminal vasodilatation, but I would doubt it. You will have noticed, however, that a short period of ischemia is followed by reactive hyperemia.

COMROE. But, Dr. Potter, you talked about capillary engorgement, didn't you?

POTTER. Yes, total engorgement of the entire vascular bed of the lung.

DAWES. This is seen after death?

POTTER. Yes.

COMROE. Capillaries themselves are said to be resistant to passive distension by an increase in their transmural pressure. Dr. Norman Staub in our department has been doing a study to determine whether capillaries

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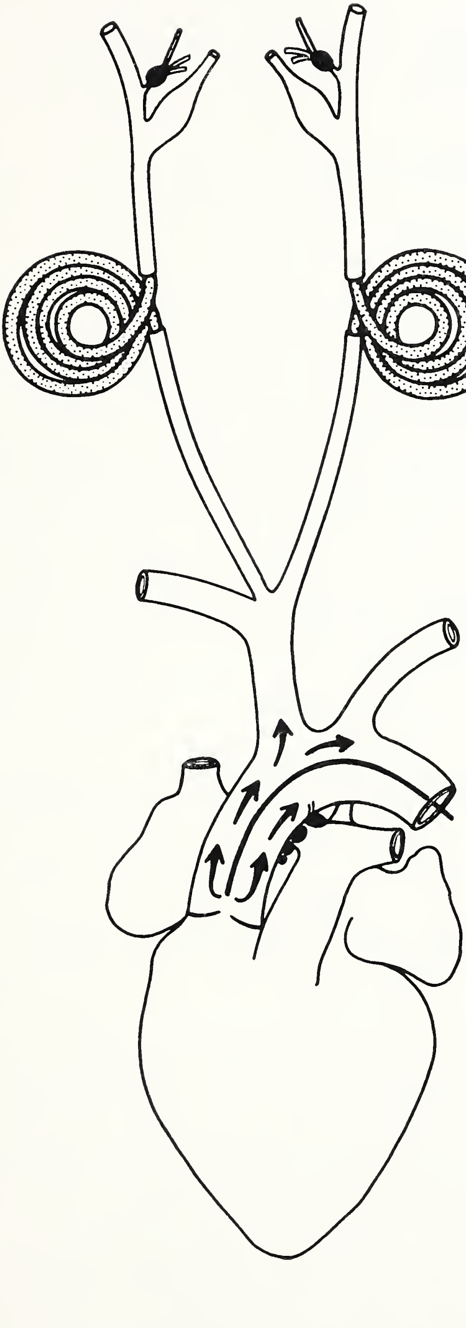
FIGURE 87.—Temporal separation of aortic and carotid bodies. A catheter is passed up the abdominal aorta of a dog until it lies in the ascending aorta just beyond the aortic valves. Each common carotid is clamped, severed in midneck, and a coil of wide-bore plastic tubing is inserted to reunite the two ends. Stimulant chemicals injected through the catheter reach the aortic bodies (*black ovals between the aorta and pulmonary trunk*) in less than a second but do not reach the carotid bodies for another 30–60 seconds. The effects of brief aortic body stimulation are thus complete before the effects of carotid body stimulation begin. Reprinted, by permission, from Comroe, J. H., and Mortimer, L.: The respiratory and cardiovascular responses of temporally separated aortic and carotid bodies to cyanide, nicotine, phenyldiguanide, and serotonin. *J Pharmacol Exp Ther 146: 33–41 (Oct) 1964.*



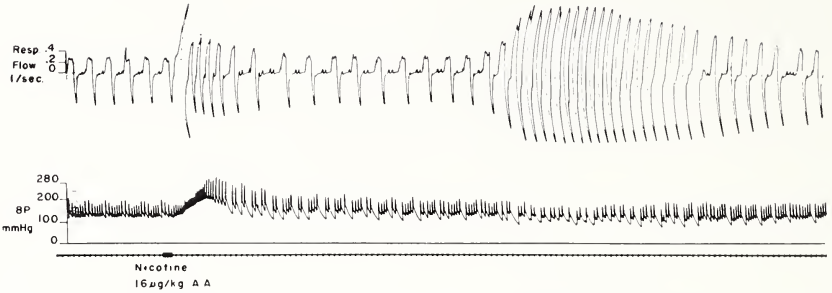


Figure 88.—Effects of aortic and of carotid body stimulation. A single injection of 16 µg/kg of nicotine into the ascending aorta of a dog produces an immediate tachycardia, hypertension, and hyperpnea (aortic body response). Because of the delay coils in the carotid arteries (see fig. 87), the carotid body response does not occur until 60 seconds later; it consists of more intense hyperpnea but bradycardia and hypotension. Reprinted, by permission, from Comroe, J. H., and Mortimer, L.: The respiratory and cardiovascular responses of temporally separated aortic and carotid bodies to cyanide, nicotine, phenyldiguanide, and serotonin. *J Pharmacol Exp Ther 146: 33–41 (Oct) 1964.*

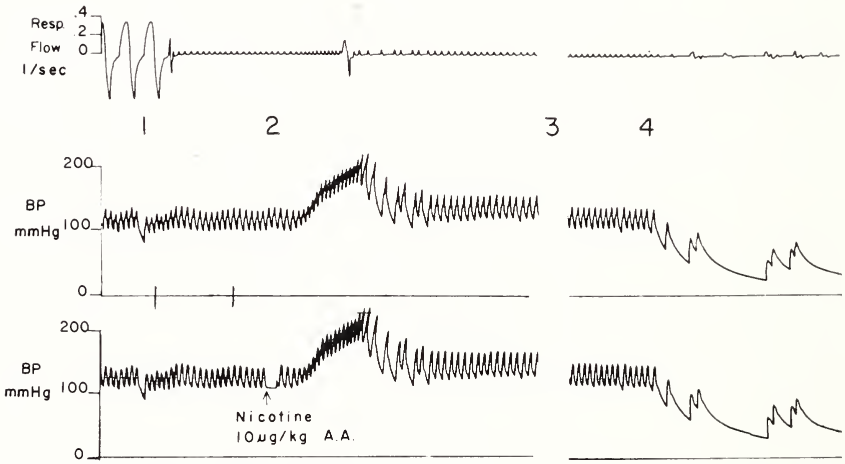


Figure 89.—Effects of aortic and of carotid body stimulation in an apneic dog. At *1*, the respiratory muscles are paralyzed by intravenous succinylcholine. At *2*, nicotine is injected into the ascending aorta; the aortic body response begins within 2 seconds and consists of tachycardia and hypertension. After a long delay (45″ of the record has been deleted at *3* to save space), the carotid body response occurs at *4;* it consists of marked bradycardia and hypotension. Two blood pressure tracings are included to show that the plastic coils used (see fig. 87) offer little resistance to blood flow. The upper blood pressure tracing is from a strain gauge on the cardiac side of the coil. Reprinted, by permission, from Comroe, J. H., and Mortimer, L.: The respiratory and cardiovascular responses of temporally separated aortic and carotid bodies to cyanide, nicotine, phenyldiguanide, and serotonin. *I Pharmacol Exp Ther 146: 33–41 (Oct) 1964.*

can dilate following intense venous constriction or whether they dilate only when there is endothelial damage. Many years ago, Soma Weiss showed pictures of capillaries so large that there were three or four red blood vessels abreast. This was in patients with chronic mitral stenosis. In acute states, Dr. Staub found evidence of capillary enlargement only when there was capillary wall damage or extreme pressure change.

HEART RATE AFTER BIRTH

Caldeyro-Barcia. The continuous record of heart rate in the human newborn infant shows a transient rise after delivery.[40]

Figure 90 shows the average values in eight infants born after complicated labors. In this group the heart rate rose, reaching 190 beats per minute 10 minutes after delivery and then slowly descended. One hour after delivery, it was 150 beats per minute. The average values of eight newborn infants with uncomplicated labor and delivery are also shown. In this group, the heart rate showed a rapid rise immediately after delivery, and the fall was much more rapid than in the distressed group. In about 25 minutes, the heart rate descended to 145 beats per minute. The rate then descended more slowly, and in about 1 hour it had stabilized at 135 beats per minute.

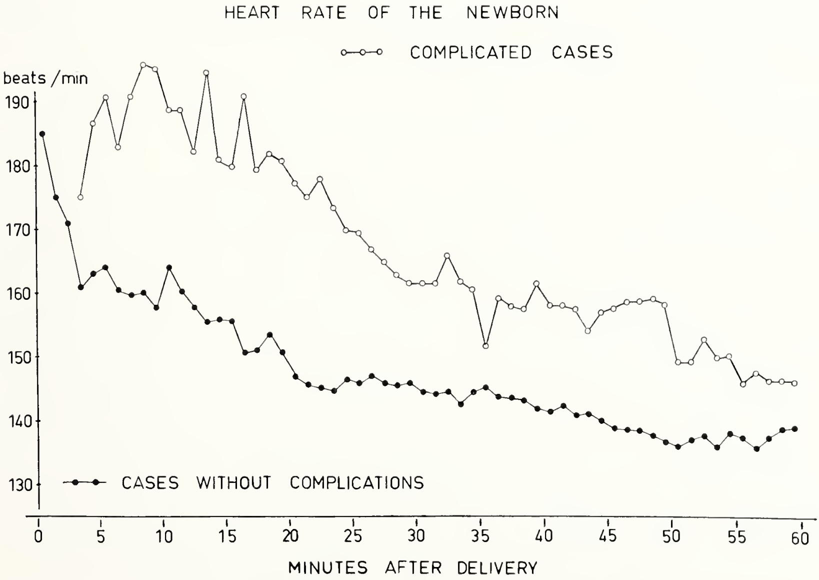


Figure 90.—The "rebound tachycardia" occurring in the newborn is more delayed and marked after complicated labors with fetal distress than in the control group. Reprinted, by permission, from Fonseca, D., Méndez-Bauer, C., and Caldeyro-Barcia, R.: The heart rate of the newborn. To be published.

We have designated this postnatal rise in heart rate as "rebound tachycardia." A similar phenomenon occurs *in utero* when the fetus is recovering from a period of distress, such as that caused by very strong and frequent uterine contractions.

OXYGEN CONSUMPTION IN THE NEWBORN

CROSS. If we examine the oxygen consumption or heat production of a warm-blooded animal and change the environmental temperature, we shall find a range of environmental temperature covering a few degrees centigrade where the oxygen consumption is minimal. This is the neutral environmental temperature. When the environmental temperature is lowered below this, the oxygen consumption will begin to rise. This is known as the lower critical temperature.

When discussing the neutral temperature of the infant, it is quite inadequate to give a single dry bulb reading. We need to know the wet and dry bulb temperatures, the nature and temperature of the material on which the infant is lying, and whether it is subject to radiant heating or can easily radiate its own heat to the walls of the chamber or the room. If the air speed is very high, this also needs to be mentioned. Precise statements must be made about the clothes the infant is wearing. For all these reasons there are apparently large discrepancies among investigators as to the neutral environmental temperature of the newborn infant.

In the full-term newborn infant, the neutral environmental temperature in a low humidity is perhaps between 35° C. and 38° C. Immediately after birth, oxygen consumption is around 4.5 cc/kg/min and will only increase by 50 percent when the environmental temperature is dropped to 28° C. Twenty-four hours later, however, the oxygen consumption at the neutral environment will have increased by some 40 percent, and the same fall in the environmental temperature will increase oxygen consumption by 100 percent. Figure 91 illustrates in one baby, both the oxygen consumption at the neutral temperature and the response to a cool environment. The changes illustrated here for this one baby are somewhat greater than those seen in a group of infants; thus, in this infant, the oxygen consumption increased almost 75 percent above that seen at the neutral environment, whereas a 40 percent increase was seen in a large group of infants. The low metabolic rate at birth and the somewhat limited increase in oxygen consumption in response to a cold stimulus explains the fall in body temperature which is seen in almost all infants immediately after birth.

This is not a new phenomenon in mammalian physiology. It was actually in Benedict's original work [41] and has been described in a number of subjects as well as in the human. The magnitude of response, however, was much greater than we had expected.

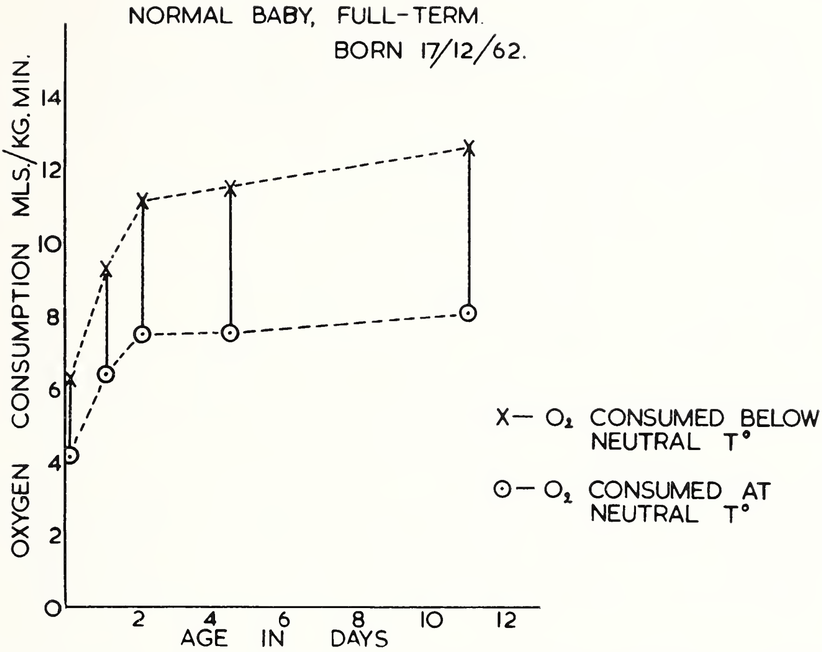


Figure 91.—Measurements of oxygen consumption of a newborn infant determined at different ages. ⊙=oxygen consumption at the neutral environmental temperature. X=oxygen consumption with a similar cold stress (about 8° C.) on different days. Reprinted, by permission, from Cross, K. W.: Respiration and oxygen supplies in the newborn. In *Handbook of Physiology, Respiration.* Washington, D.C., American Physiological Society, 1965, sect 3, vol 2, chap 52, pp 1329–1344.

In the premature infant, we did not find such an abrupt increase in metabolic rate after birth. It would seem that there is a gradual rise in the minimal oxygen consumption and a steady increase in the response to a cool environment.

Figure 92 shows the data collected from Spector's *Handbook of Biological Data.*[42] This is the minimal oxygen consumption per kilogram of body weight shown plotted against the weight in kilograms of a variety of animals. The line is drawn by eye, and in figure 93 the panel between the weights of 1 kg and 10 kgs is magnified, and the data from some full-term babies and two premature babies are plotted upon it. The full-term babies were examined within an hour or two of birth and again at about 24 hours. The thick line represents the mean results from a group of these babies examined at birth, at about 24 hours, and at about 4½ days of age. On the left side of the figure are a number of readings taken on two premature babies examined over a period of several weeks. It would appear that the oxygen consumption of all these infants is low at birth, perhaps approximat-

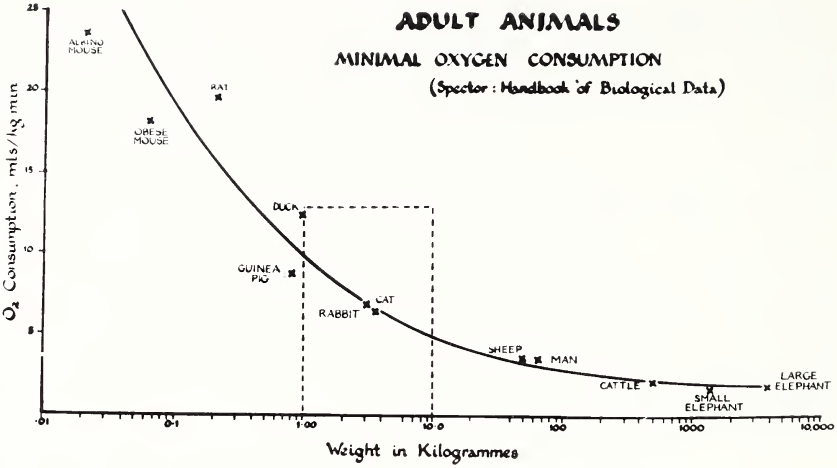


Figure 92.—Oxygen consumption of a wide variety of animals, species plotted against the weight. Note the logarithmic scale of weight. The line through the points is drawn by eye. Reprinted, by permission, from Cross, K. W.: A baby's first breaths. In *Proceedings of The Royal Institution of Great Britain 40(182): 12–26, 1964.*

ing that of the mother per kilogram of body weight. Over a different period of time the babies seem to find their place on the "adult curve" as delineated in figure 92.

The question is: What is the stimulus that makes the metabolic rate at the neutral environmental temperature increase in the first 24 hours of life? The metabolic rate is not affected if the baby is given high oxygen to breathe. There is one other bit of evidence from a baby with cretinism. Both before and after treatment, the baby seemed to have a normal response to a cold stimulus, but the level of oxygen consumption was raised a great deal after treatment with thyroxin. It is difficult to draw a clear conclusion from this, but it is perhaps worth putting in as evidence when one is considering the mechanisms whereby the baby raises his metabolic rate at the neutral environment after birth.

Silverman. Were the deep body temperatures of the premature infants lower than those of the full-term infants?

Cross. They tended to be lower. I believe they were all about 35° C.

Silverman. How long did the cold stress last?

Cross. The apparatus [43] is one in which we can change the environment quickly and get to a steady-state quickly. Each particular temperature was maintained after a steady-state for 10 minutes or so.

Caldeyro-Barcia. Is the lower limit of your neutral temperature zone about 34° C?

Cross. Yes, but it varies in different babies.

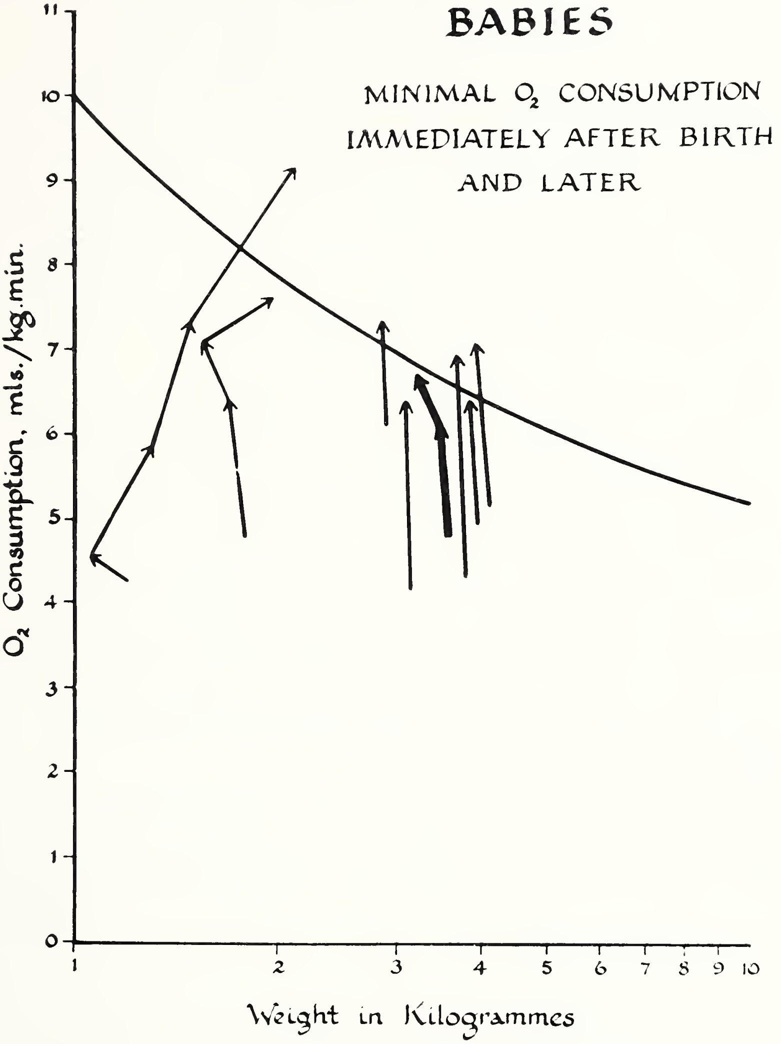


Figure 93.—The line of figure 92 redrawn for the weight range of 1 to 10 kgs. Between the weights of 3 and 4½ kgs, the arrows join the point of minimal oxygen consumption for five babies at birth and at about 24 hours of age. The thick arrow shows the oxygen consumption immediately after birth, at about 24 hours, and at an average age of 4½ days, for a group of full-term infants. Between the weights of 1 and 2 kgs, the oxygen consumption is shown soon after birth, and over several weeks, in two premature infants. Reprinted, by permission, from Cross, K. W.: A baby's first breaths. In *Proceedings of The Royal Institution of Great Britain 40(182): 12–26, 1964.*

CALDEYRO-BARCIA. Since, at this temperature, the oxygen consumption reaches its lowest values, do you think that this would be the best environmental temperature in which to keep the babies?

CROSS. Dr. Silverman's work [44] is most relevant to this. It undoubtedly seems correct that a warm environment is a good thing for the small premature baby. We still do not know what would happen if a baby were kept in a neutral environment from the moment of birth. Have animals been brought up in a neutral environment?

DAWES. Monkeys reared from within an hour or two of birth in a neutral thermal environment (35° C.) increased their minimal O_2 consumption from 8 to 9 ml/kg/min up to about 16 ml/kg/min over the first 10 days of life.[45]

CROSS. And they did have a short spell of not being in a neutral environment?

DAWES. For half an hour to an hour. When a monkey is delivered, it is wet and you cannot avoid some evaporative heat loss and hence some cooling.

SILVERMAN. I would like to pursue the point concerning the difficulty of using ambient air temperature as a measure of the thermal demand of the environment. It is an incomplete physiologic measurement, since heat exchange between the infant and his surroundings is influenced by a number of factors, including air movement, humidity, wall temperature, and posture. Moreover, in very small subjects, these influences are likely to be exaggerated. The use of air temperature as a reference point has led to a certain amount of confusion in the interpretation of studies of thermal influences in the newborn, and there is misunderstanding about the definition of the so-called neutral environmental temperature.

The ideal homeotherm is able to maintain a normal body temperature with minimum expenditure of energy when in a neutral environment. The small newborn infant, in the environment which is usually provided for it, often exhibits a low or falling deep body temperature, and the question arises about the limits of homeothermy in these circumstances. We have made some observations that bear on this point.

Figure 94 shows Mount's observations on body temperature in a group of newborn piglets subjected to a standard cold exposure (5° C.) for periods up to 8 hours. He noted that although many of the newborn piglets were able to defend the deep body temperature for the entire period, others were unable to maintain homeothermy for even 3 hours in the face of this demand.

We exposed each of a group of small infants ($\leq$1,500 gm) to three thermal conditions: 1, abdominal wall temperature maintained at 36° C. by a servo-controlled electropane; 2, air temperature 34° C.; and 3, air temperature 32° C. The order of exposure was randomized. Figure 95 shows the deep colonic temperatures after complete equilibrium of infants in the three

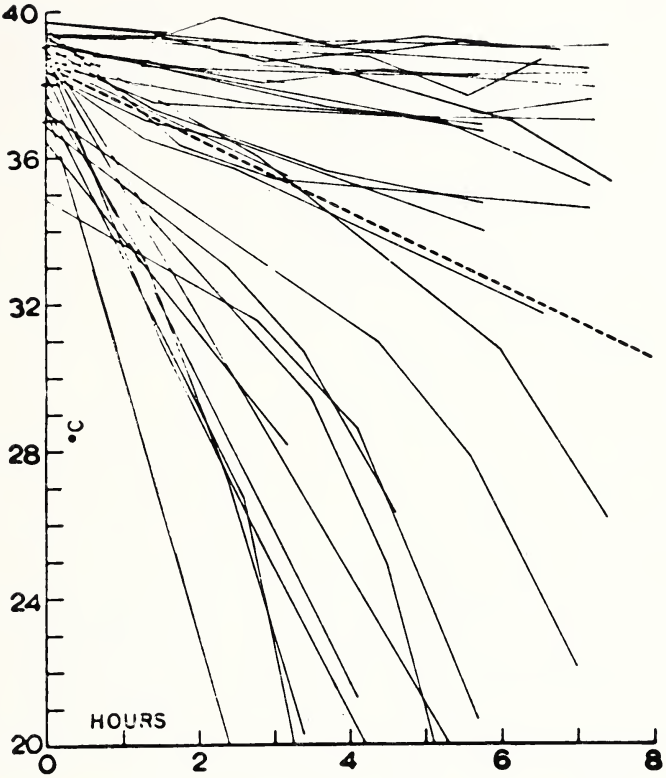


FIGURE 94.—Body temperature and cold exposure in piglets. Rectal temperatures are shown of newborn piglets exposed to 5° C. ambient temperatures for intervals up to 8 hours. Dotted line indicates a rate of cooling of 1° C. per hour. Reprinted, by permission, from Mount, L. E.: Responses to thermal environment in newborn pigs. *Fed Proc 22: 818–823 (May–June) 1963.*

conditions, arranged here in a uniform order. Half of the infants were able to maintain deep body temperature above 35° C. in the two air-controlled environments, whereas others exhibited marked falls in both 34° C. and 32° C. conditions. These environmental conditions served to discriminate the infants, as noted by Mount in piglets exposed to much cooler conditions.

Infants who were able to prevent a marked fall of deep body temperature in 34° C. and 32° C. ambient air (fig. 96) maintained a large temperature gradient between core (colon) and periphery (foot) and exhibited an increase in oxygen consumption. On the other hand, in infants whose deep body temperatures fell below 35° C. in the same ambient conditions (fig. 97), colon and foot gradients were small, and oxygen consumption was either unchanged or fell.

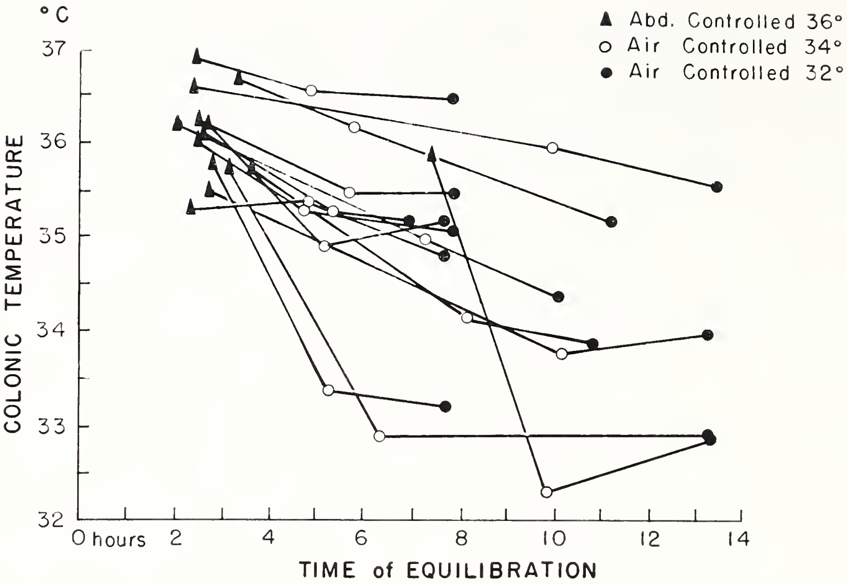


FIGURE 95.—Colonic temperature at equilibrium under three thermal conditions. The colonic temperatures and the (cumulative) time to reach equilibrium for each infant are shown under three controlled conditions. ▲=abdominal wall controlled at 36° C. by radiant heat; ○=ambient air controlled at 34° C; ⊙=ambient air controlled at 32° C. Reprinted, by permission, from Silverman, W. A., and Agate, F. J., Jr.: Variation in cold resistance among small newborn infants. *Biol Neonat 6: 113–127, 1964* (S. Karger, Basel/New York, publisher).

The relationship between average skin temperature and oxygen consumption (fig. 98) in this group of small infants was consistent with the notion that although 34° C. and 32° C. air environments, which have been referred to as the neutral environmental temperature for newborn infants, were within the thermoregulatory range of some small infants, these conditions were beyond the cold limits of others of comparable body size.

In small newborn infants it may be more satisfactory to refer to the neutral thermal state in terms of the distribution of deep and superficial body temperatures, as opposed to a neutral environmental temperature.

SEGAL. Dr. Silverman, could you elaborate on the physiological mechanisms relating to the data which have been derived using an infrared emitter? Are there any studies to show the effects of a similar servo appliance which would heat the circulating air rather than cause the emission of infrared energy? Also, what is the explanation for the differences between the mechanisms of action of the servo system and the constant temperatures of groups 2 and 3?

SILVERMAN. We haven't enough information on air heating to answer your question.

COMROE. Was there a problem of vasoconstriction or no vasoconstriction?

SILVERMAN. No, all infants were capable of maintaining marked peripheral vasoconstriction.

OLIVER. Several years ago, Dr. Karlberg and I induced hypothermia in a few term infants who had been given chlorpromazine (which kept them asleep). Their body temperatures fell from 37° C. to as low as 33° C. for periods of several hours. During this time oxygen consumption doubled,

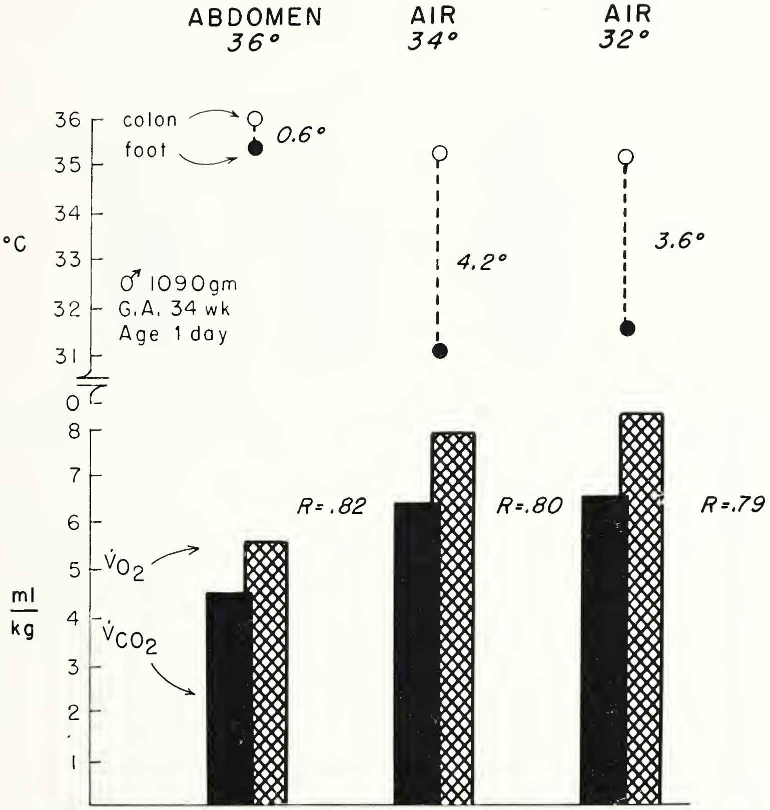


FIGURE 96.—Successful homeothermy on exposure to cold. Colonic temperature, foot temperature, colon:foot difference, oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide excretion ($\dot{V}_{CO_2}$) and respiratory exchange ratio ($R=\dot{V}_{CO_2}/\dot{V}_{O_2}$) are shown for an infant who was able to prevent a marked fall in colonic temperature when exposed to 34° C. (air) and 32° C. (air) incubator as compared with radiant heat-controlled condition. Reprinted, by permission, from Silverman, W. A., and Agate, F. J., Jr.: Variance in cold resistance among small newborn infants. *Biol Neonat 6: 113–127, 1964* (S. Karger, Basel/New York, publishers).

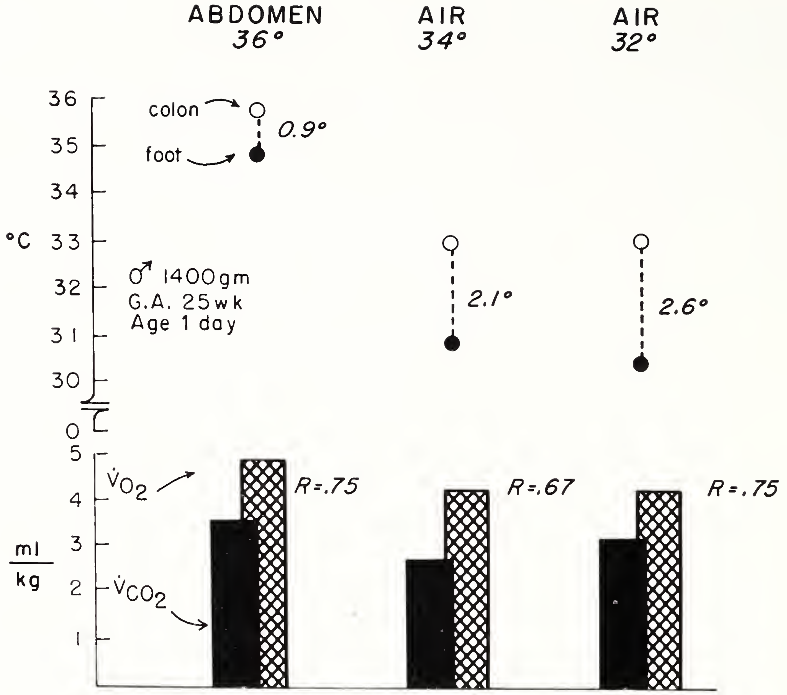


FIGURE 97.—Unsuccessful homeothermy on exposure to cold. See figure 96. Reprinted, by permission, from Silverman, W. A., and Agate, F. J., Jr.: Variation in cold resistance among small newborn infants. *Biol Neonat 6: 113–127, 1964* (S. Karger, Basel/New York, publishers).

and this increase was maintained until the environment was rewarmed. Thus, the response to cold is related, in part, to size and, perhaps, to maturity.

We, like Drs. Cross and Silverman, have studied the relationship of the thermal environment to heat production (fig. 99). We used an open-circuit method for measuring gaseous metabolism. The infants, all at term, ranged from 1 to 8 days of age. They were absolutely quiet, had been sleeping for a minimum of 20 minutes, and were unclothed. The relative humidity in the metabolism chamber was about 50 percent; radiant losses were minimized. All had body temperatures between 36.5° C. and 37.2° C.

Under these circumstances (which were very similar to those described by Brück [46]), the neutral environmental temperature was between 32° C. and 34° C. Oxygen consumption rose at lower environmental temperatures.[47]

At neutral thermal conditions, oxygen consumption does not change significantly between the first and the eighth days of life, the mean value being 6 ml/kg/min.[47] It is noteworthy that this value, which is in agreement with Brück and the group at Columbia, is lower than that of Cross. This suggests the thermal conditions in his infants were below the lower critical temperature. We have not studied infants during the first day. Finally, it should be mentioned that the rise in metabolism that occurs in the term infant, when he is in a cool environment, can be totally inhibited by breathing 15 percent oxygen.[48] I believe Dr. Dawes may comment further on the duration of the inhibitory effect of 15 percent oxygen.

COMROE. The last three speakers have discussed the increase in oxygen consumption with lowering of temperature, but they have not discussed why the oxygen consumption goes up. The obvious point is whether the newborn infant shivers.

OLIVER. No. It does not.

COMROE. Is there invisible shivering that might be detected by electrodes?

SILVERMAN. There is no visible shivering. We have not performed electromyography.

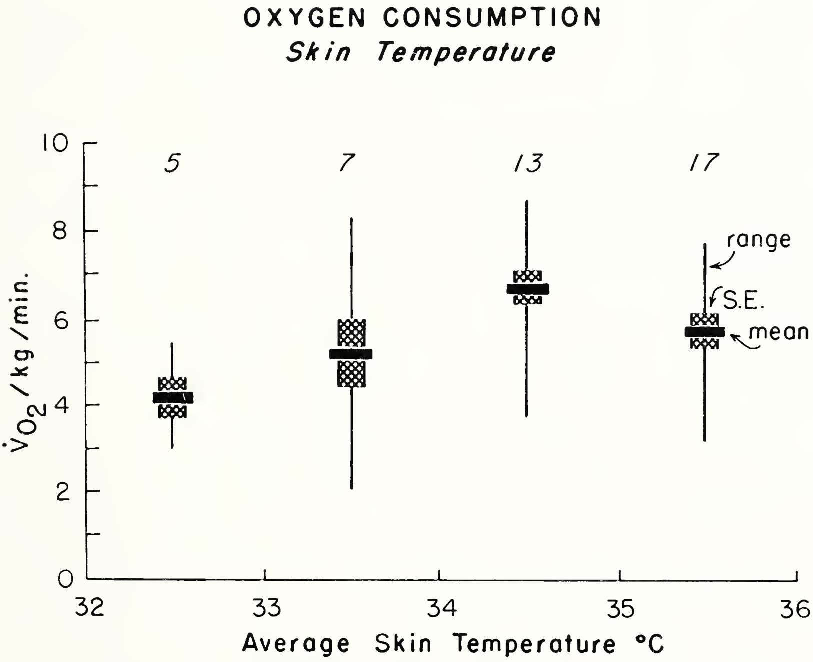


FIGURE 98.—Metabolism and skin temperature. Mean (standard error of mean and range) minute oxygen consumption ($\dot{V}_{O_2}$) is shown at each (weighted) average skin temperature (grouped by 1° C. intervals) among infants in radiant heat and air-controlled incubators. Reprinted, by permission, from Silverman, W. A., and Agate, F. J., Jr.: Variation in cold resistance among small newborn infants. *Biol Neonat 6: 113–127, 1964* (S. Karger, Basel/New York, publishers).

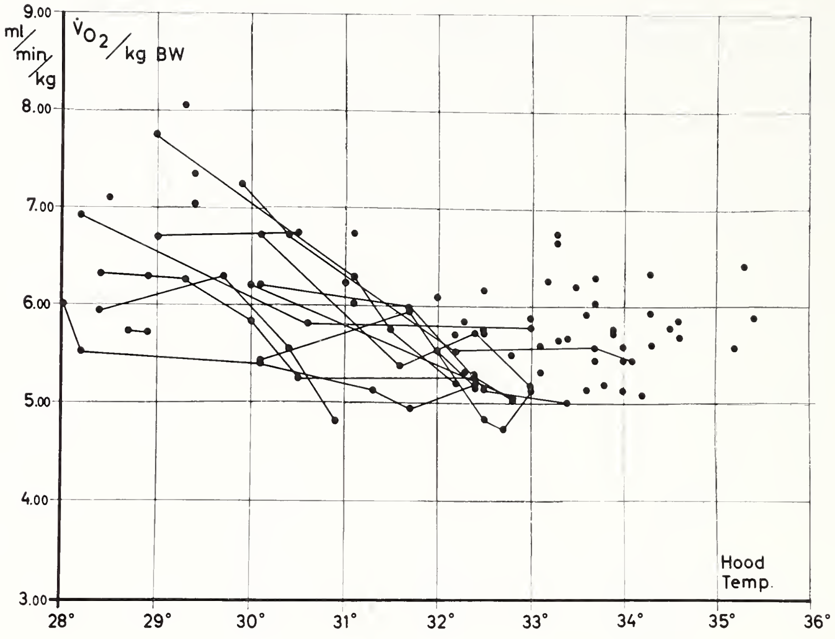


FIGURE 99.—The relationship of oxygen consumption to environmental temperature in term infants. (See text for details.) Reprinted, by permission, from Oliver, T. K., Jr.: Thermoregulation of the newly born. In *Reports of Ross Conferences on Pediatric Research, Supplement No. 2.* S. G. Thompson, editor. Columbus, Ross Laboratories, 1964, pp 15–18.

CROSS. There are no muscle action potentials on electrocardiograms during cold exposure.

COMROE. What is the increase in oxygen consumption due to? Why is there an increased energy production? Is this a reflex?

DAWES. It is well known that oxygen consumption increases greatly on exposing newborn animals or babies to cold. Intravenous infusions of norepinephrine have a similar effect. The question is: What is the mechanism?

In the newborn rabbit, O_2 consumption in a neutral thermal environment is about 18 to 20 ml/kg/min and increases about threefold on exposure to cold. Total neuromuscular paralysis by gallamine does not abolish this response [49] which therefore cannot be due to shivering.

In the spring of 1963, Michael Dawkins, while doing autopsies on newborn rabbits for other purposes, noted that the brown fat pad which encircles the neck and runs down between the scapulae decreased greatly in size over the first 7 to 10 days of life, during which time previous experiments had shown that intravenous infusions of norepinephrine had a gradually decreasing effect on O_2 consumption.[50] Dawkins and Hull [51] subsequently found that on exposing newborn rabbits to cold, or on infusion of norepinephrine, the subcutaneous temperature over the brown fat pad was maintained or increased above that recorded beneath the skin elsewhere, in the rectum, or near the liver. The brown fat became 2° C. or 3° C. warmer.

If you expose a newborn rabbit to cold and then give it a low O_2 mixture to breathe, the increase in O_2 consumption is abolished. The temperature over the fat pad falls rapidly and soon reaches that of the rectal and other subcutaneous thermocouples. When air is then given to breathe, the temperature of the fat pad begins to rise rapidly—before that of any of the other places studied—so that the differential temperature between the brown fat and elsewhere is even greater.

Brown fat, according to Dawkins and Hull, amounts to about 5 percent of the body weight of newborn rabbits, and *in vitro* it has a resting O_2 consumption of about 20 times that of adult white fat. Exposure to cold, or infusion of norepinephrine, caused a very small, statistically insignificant rise in plasma-free fatty acids but a very large rise in plasma glycerol. This, and other evidence, has suggested that most of the free fatty acid released is metabolized in the brown fat itself.

COMROE. Metabolized to what and for what?

DAWES. Lipolysis and the subsequent degradation is a highly exothermic reaction.

COMROE. But what point is served by having the fatty acids burn in the brown fat? The level of free fatty acids need not rise in the blood to any measurable degree if they are burned in the body as fast as they are liberated. One can tell this by tracer and turnover studies. The fact that free fatty acids don't rise in the blood doesn't mean that free fatty acids are being burned in the brown fat itself.

DAWES. The observations are consistent with fat being burned rapidly somewhere.

VILLEE. I think it would have to be burned in other tissues as well as in the brown fat, if one is to account for a threefold increase in the overall oxygen consumption of the fetus or newborn because the amount of brown fat is just too small in comparison to the mass of the whole organism.

LEVINE. If one takes into consideration the fact that the small premature baby has only 1 percent fat in its total body, this seems even more farfetched.

COMROE. It should be stated that the fat content of different animals varies tremendously at birth, and one has to specify the animal in a situation such as this.

DAWES. In the rabbit, at least, there is an extremely high temperature differential.

COMROE. Wouldn't the simple fact that there was a reaction going on in the fat, which was producing free fatty acids from triglyceride—wouldn't that in itself raise the temperature in active tissue?

Villee. The simple lipolysis of triglyceride to glycerol and fatty acids would not result in any significant production of heat. It is only after the glycerol and fatty acids have further metabolized to carbon dioxide and water that heat would be liberated.

Clements. Does curarization modify these results?

Dawes. Curare is a bad drug to use for this purpose, because it blocks autonomic ganglia as well. Curare does not block the increase in O_2 consumption caused by norepinephrine. Gallamine produces neuromuscular blockade, but it does not abolish the metabolic response to cold.

Villee. There is a large body of experiments demonstrating effects of norepinephrine and other drugs on adipose tissue, particularly the adipose tissue of the epididymal fat pad. If the brown fat responds to norepinephrine by releasing free fatty acids, which could then be taken up by other tissues and metabolized, I think one could account for the overall increase in oxygen consumption that is observed.

Comroe. That's fine, but what about his local increase in temperature?

Villee. There would be an initial increase in oxygen consumption locally, too.

Dawes. I would like to think that the increase in metabolism in brown fat was large.

Villee. But not from lipolysis.

Comroe. If norepinephrine is doing the liberating, as everyone thinks, what does it do to the blood flow to brown fat? Does it decrease it to a trickle?

Dawes. I wish we could measure the blood flow through brown fat in a rabbit weighing 60 gm. We also want to know how much of the total increase in O_2 consumption occurs in the brown fat.

Comroe. Why do you think that anoxia blocks this? Since anoxia activates the sympathetic nervous system, presumably norepinephrine should be liberated.

Dawes. I think the most likely explanation is that hypoxia reduces the amount of O_2 carried by the arterial blood. It may also limit cardiac output. Quite a small hemorrhage will reduce O_2 consumption in a newborn rabbit exposed to cold.

Comroe. Let's switch for a moment to the rat. Dr. Hugo Chiodi, who works at high altitudes in South America, made an observation some years ago that at about 4,800 meters altitude, dogs, cats, mice, and other animals were plentiful, but there were no rats! He then tried to breed rats at high altitudes and found that the newborn rats all died within the first 10 days or so. They all died with massive fatty infiltration of the liver. He has been able to reproduce this by giving rats low concentrations of carbon monoxide to breathe at sea level. There seems to be considerable increase of triglyceride fatty acid in the blood as a result of the anoxia. Possibly, because of a metabolic defect in the liver of the newborn rat, it cannot handle these fatty acids, and it dies with a fatty liver.

DAWES. The newborn rat has very little fat, and its oxygen consumption on exposure to cold at sea level is very limited. It is only after about 48 hours that it begins to show an increase in oxygen consumption on exposure to cold. Over the following 10 days, its maximal oxygen consumption on exposure to cold steadily increases. I don't know the explanation for this. One can only guess that, being born with little fat, it has little to burn up rapidly, and that it acquires fat from its mother's milk. Whether it turns this into brown fat I do not know.

COMROE. Have you tried the effect of nicotinic acid?

DAWES. Why?

COMROE. Nicotinic acid in some species specifically blocks that action of norepinephrine or sympathetic stimulation which normally liberates free fatty acids from fat tissue without producing sympathetic blocking effects elsewhere.

DAWES. David Hull has given a drug called Pronethalol, which blocks the increase in heart rate and fall of blood pressure caused by isoprenaline. It also blocks the rise in O_2 consumption caused by infusion of norepinephrine without blocking the rise in O_2 consumption on exposure of a newborn rabbit to cold.

Therefore, whatever else may be the reason for the rise in oxygen consumption of the newborn rabbit on exposure to cold, it is not due to liberation of norepinephrine into the circulation. Naturally, this does not exclude the possibility that norepinephrine is being released locally in or near the fat cell in sufficient concentration to be effective. Now, do you know where or how nicotinic acid would work?

COMROE. Presumably, it is a specific blocking agent at the fat cell.[52]

CLEMENTS. This is the white fat only?

COMROE. Yes. I don't know about the brown fat.

SILVERMAN. You wouldn't say that the whole brown adipose tissue story ends with the consideration of its function as a fat depot, since this tissue is apparently able to carry on a very active metabolism.

DAWES. No. Certainly, I agree. Furthermore, it is now known to appear in hibernating animals and on cold acclimatization in adult rats.

SILVERMAN. The total cold-induced nonshivering thermogenesis cannot be accounted for by this tissue. There is evidence of increased heat production in other organs, notably in the liver and in the gut.

DAWES. Yes. One would like so much to know proportionately what organs are playing a part.

SILVERMAN. The evisceration experiments of Scopes and Tizard [50] indicated that there is a contribution from other sites. Dr. R. E. Smith [53] has proposed that the anatomic location of this tissue around the great vessels is important. The notion that brown adipose tissue warms cold blood from the periphery before it reaches the heart and central nervous system is intriguing.

COMROE. Why is brown fat brown?

VILLEE. Because it has a lot of active cytoplasmic material and relatively little stored triglycerides, much less so than white fat.

COMROE. In other words, if you liberated the free fatty acids from white fat and then looked at the tissue, it would be brown fat?

VILLEE. It would certainly be browner than it is with all the fat in it.

FREMONT-SMITH. Is there a pigment in it?

SILVERMAN. Cytochromes have been suggested. Some have attributed its color to a rich blood supply.

COMROE. But all fat tissue has a rich blood supply. This has long been misunderstood. On the basis of weight of its protoplasm, fat tissue has one of the richest blood supplies in the body.

VILLEE. Fat tissue also has a very high rate of metabolism, when one makes suitable corrections for the amount of metabolically inactive stored lipid.

SOROKIN. Cytochemically, brown and white fat are qualitatively similar.[54] In organ cultures, brown fat can be grown to resemble white fat.[55] Nevertheless, in cells of brown fat, mitochondria have a highly ordered inner structure with numerous cristae.[56] In cells of white fat, mitochondria are simpler, but cytoplasmic membrane systems are more prominent than in cells of brown fat.[57] It has been thought that the color of brown fat is ascribable to the concentration of respiratory pigments in its mitochondria and to the blood in its rich vascular bed.

RAMSEY. Is there a variation in distribution throughout fetal and adult life? Do you get excess deposition of white fat with increasing age?

SOROKIN. In its histogenesis, white fat passes through a stage at which its cells resemble those of brown fat; their fat deposits are multilocular. Such cells later become unilocular; hence, there is an apparent relative decrease in brown fat deposition with increasing age.

COMROE. What significance, Dr. Silverman, do you place on the fact that one animal increases its energy production and maintains its heat and another one cannot? What is the mechanism involved here?

SILVERMAN. One can only speculate about the mechanism. Variations in the amount of brown adipose tissue, for example, might account for success or failure to maintain homeothermy on exposure to cold.

VILLEE. It seems clear that there are considerable variations within a species in this regard.

OLIVER. With respect to thermal control, I think it is important to make a point of some clinical importance. Two groups of investigators have studied the relationship of mortality of premature infants to environmental temperature.[58, 59] Abdominal skin temperature was maintained at 36° C. using a radiant heating device controlled by a servo system with a thermocouple taped to the abdomen. Control infants of similar weight were nursed in incubators with air temperature at about 32° C. Survival was significantly higher in the former babies.

KARLBERG. May I throw out a chain of loose thoughts ending with a question to Dr. Clements? At high altitude, rats are not able to metabolize liberated fat. In human newborn infants, infusion of norepinephrine increases the metabolic rate.[60] This thermogenic response may be related to mobilization of free fatty acid.

In human newborn infants, the thermogenic response to low environmental temperature is aborted by breathing 15 percent oxygen.[48]

In human newborn infants with disturbed respiratory adaptation and who are exposed to cold, there may be increased amounts of free fatty acid circulating in the blood. Can this free fatty acid destroy the surface-active material lining the alveolar wall, thereby causing idiopathic respiratory distress syndrome?

CLEMENTS. We simply don't have the data at this point to give a proper answer. I can only speculate. It is known from *in vitro* studies that lung slices have a voracious appetite for free fatty acids, especially palmitic. They take them up from the incubation medium and incorporate them into complex lipids.

We also know, in terms of the chemical anatomy, that there is an exceptionally large quantity of phospholipid and that much of the free fatty acid which is being taken in is headed for incorporation into the phospholipid fraction.

I think it is still problematic whether or not excess fatty acids being carried around in the plasma could, in fact, penetrate the alveolar barrier and appear on the air side in a position to interfere with already formed surface-active material and, in that way, lead to an abnormally high and deleterious surface tension.

The observations which come closest to bearing on this are those connected with the pump syndrome following cardiopulmonary bypass. Passage of blood through the external circuit is said to denature the plasma proteins, especially the lipoproteins, and free neutral lipids from them. Whether the pump syndrome exerts its deleterious effect as a direct consequence of action at the alveolar surface, or whether there are fat microemboli and a diffuse kind of arterial occlusion, is not known at present.

SILVERMAN. While we are speculating, I should like to bring up the matter of lipid mobilization and bilirubin distribution in the neonate. It has been shown that fat infusions, or a fatty meal, will lower the plasma concentration of bilirubin. It is assumed that the distribution of bilirubin between the vascular and extravascular tissues is altered. In the Gunn rat, a lipid infusion is followed by a fall in plasma bilirubin concentration and an increased incidence of brain damage (kernicterus).

Oliver. This is presumably because fatty acids can displace bilirubin from binding sites with albumin. The unconjugated, unbound bilirubin which is lipid-soluble can then readily traverse the membrane of brain cells, causing brain damage.

Clements. This leads back to a point that I failed to mention. It might well be that the level of plasma protein could play a significant role in whether or not there is lung damage when the circulating free fatty acid is increased. Is that reasonable, Dr. Villee?

Villee. Yes, I think so. The level of plasma proteins is lower in the premature infant than in the term infant.

Comroe. Dr. Avery, you haven't said a word about diabetes. Does that enter into this at all?

Avery. I think it should, but I don't know enough to say anything about it except that the infant of a diabetic mother is predisposed to respiratory distress, particularly hyaline-membrane disease.

Cook. Are we certain that there is an increased incidence of respiratory distress in infants of diabetic mothers if they are compared to control infants of the same gestational age rather than of the same size?

Segal. I think it is clear that the mortality rate is higher.

Klaus. I agree. Furthermore, the total body fat content of these babies is increased. It is not an increase in total body water but an increase in total body fat.

Bruns. Among other reasons for the respiratory distress is the 25 percent incidence of toxemia in pregnancy in diabetic mothers. Therefore, when one talks about maternal diabetics and the outcome of the babies, I think it would be important to separate these two complications.

Pickering. I think it should be mentioned, also, that this syndrome can occur in a woman in whom diabetes might develop 10 or 15 years later and who will show no manifestations of toxemia at all in her pregnancy.

Smith. Diabetic mothers are usually delivered at 37 weeks, because, for almost every day the fetus stays in the uterus longer than that, there is an increased tendency for it to die *in utero*. It doesn't die *in utero* from lack of surfactant, although, as I remember, Dr. Avery had one baby who was stillborn whose lungs showed no surfactant and this was the baby of a diabetic mother. That did not explain why it died, but it might explain why other infants of diabetic mothers die. I think they do have a higher incidence of respiratory distress, whereas we do not find a very high incidence of respiratory distress in 37-week babies of nondiabetic mothers. What is the surfactant status of infants of diabetic mothers?

Avery. There is nothing special about it. In Driscoll's study [61] of neonatal deaths among infants of diabetic mothers, 71 of 95 had hyaline-membrane disease. This is a higher incidence than in any like group of babies of comparable gestational age. There was no qualitative or quantitative difference that we detected in this group as compared to others.

Smith. I do not believe that lungs from infants of diabetic mothers who died of other causes have been studied.

Comroe. Dr. Avery, have you done any followup studies on babies who have recovered from hyaline-membrane disease? Once they have recovered, are they normal?

Avery. I don't know of any large, careful study, where good clinical documentation was obtained in the newborn period and careful evaluation of pulmonary function made later. I can only tell you that in a few cases it is quite clear that they are normal.

Comroe. I am not concerned about pulmonary function only but about the body mechanisms in general—metabolism, reflexes, and so forth.

Avery. I am sure that we haven't looked into this carefully enough.

Stahlman. We have a 2-year followup on documented severe cases. The babies are intact neurologically. They are asymptomatic as far as their lungs are concerned, but three-fourths of them have abnormal chest X-rays, which the radiologists describe as pulmonary fibrosis.

Avery. Have you performed blood gases on these babies?

Stahlman. They haven't been done.

Karlberg. In Stockholm and Göteborg, we think we have saved the lives of some babies with very severe cases of idiopathic respiratory distress syndrome by using a positive pressure respirator. After several weeks, the babies have been able to breathe on their own but have retractions, tachypnea, and an abnormal chest film. The clinical picture, as well as the X-ray, has gradually improved during the following months. In one patient, a lung biopsy was performed when the baby was 6 months of age, which showed pulmonary fibrosis. The baby, however, continued to improve clinically.

Levine. May I make one comment? In view of the discussion of oxygen consumption and the role of the fatty acid metabolism, it might be interesting to do respiratory quotients on the offspring of diabetic mothers and on children who have hyaline-membrane disease to see whether there is an active fatty acid breakdown. If this were true, one should get a lower respiratory quotient than in the normal premature or well baby.

Comroe. I think it is an excellent idea. There probably would be additional ways of doing this, by means of measuring the turnover of free fatty acids.

Oliver. In the few babies in whom we infused norepinephrine,[60] we did not see changes in the respiratory quotient during the time of infusion.

Schafer. Did you measure free fatty acids?

OLIVER. No.

DAWES. Over how long an interval did you collect the gases?

OLIVER. The infusion was for periods of 20 minutes at the longest. The measurement of gaseous metabolism continued for an additional 20 to 60 minutes.

COMROE. Dr. Charles Van Duyne[62] has done survival studies in the newborn lamb. He found that in those that survive very well, norepinephrine did not necessarily release free fatty acids, even though he was pretty sure that the sympathetic nervous system did so. This is a strange observation and I don't know how to explain it at the moment.

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Acid-Base Balance and the Effects of Maternal Anesthesia and Blood Pressure; Neonatal Pulmonary Function

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Bruns. My interest in the problems of the newborn infant began many years ago when Dr. Herbert Miller suggested that the cause of premature birth might be the same agent which causes injury to the infant's lungs.

Since that time we have tried to answer the question of whether or not the respiratory distress syndrome has its origin *in utero* as a form of biochemical injury to the fetus. Our studies indicate that the biochemical injury may represent a defect in maternal-fetal oxygenation or acid-base metabolism. However, in seeking answers we have only come up with more questions.

From our measurements, the normal pH of a baby *in utero* at the moment of delivery is the same as that of its mother. Perhaps Dr. James will elucidate.

James. For several years we have believed that the fetus is usually in acid-base equilibrium with its mother. However, maternal anesthesia may influence this relationship.

One example is the influence of maternal hyperventilation during cesarean section on the acid-base balance of the fetus.[1] If the mother was given muscle relaxants and hyperventilated for 5 minutes prior to delivery of the infant, we observed that it was possible to achieve a lower pCO_2 and higher pH in the umbilical vein at birth than when normal maternal ventilation was maintained. We thought this might be a favorable way of influencing the fetal acid-base balance prior to delivery. However, it soon became apparent that the umbilical vein pCO_2 did not always fall during maternal hyperventilation. In two infants, the pCO_2 was 80 mm Hg while the mothers' was less than 17 mm Hg. These infants were clinically depressed. Because of this, we decided that any form of willful overventilation of the mother might be hazardous for the fetus.

Pregnant guinea pigs were then studied by Dr. Morishima [2] to determine the mechanisms. The animals were at term and were lightly anesthetized with a barbiturate. A treated group were hyperventilated for a period of 5 or 10 minutes before the delivery of the fetus. The higher the maternal pH, the lower was the fetal pH. All the animals from mothers who were hyperventilated were extremely depressed at birth; none breathed spontaneously. All of the controls were lively and breathed spontaneously. Maternal pH was inversely related to fetal pH (fig. 100). The relationship between the condition at birth and the gradient of pH between the maternal arterial and the umbilical vein blood revealed that very few of the piglets in the hyperventilated group scored above 7, while most of the spontaneously breathing group did. It was observed that maternal hypocapnia was associated with hypotension and we concluded that this was adversely affecting the uterine circulation.

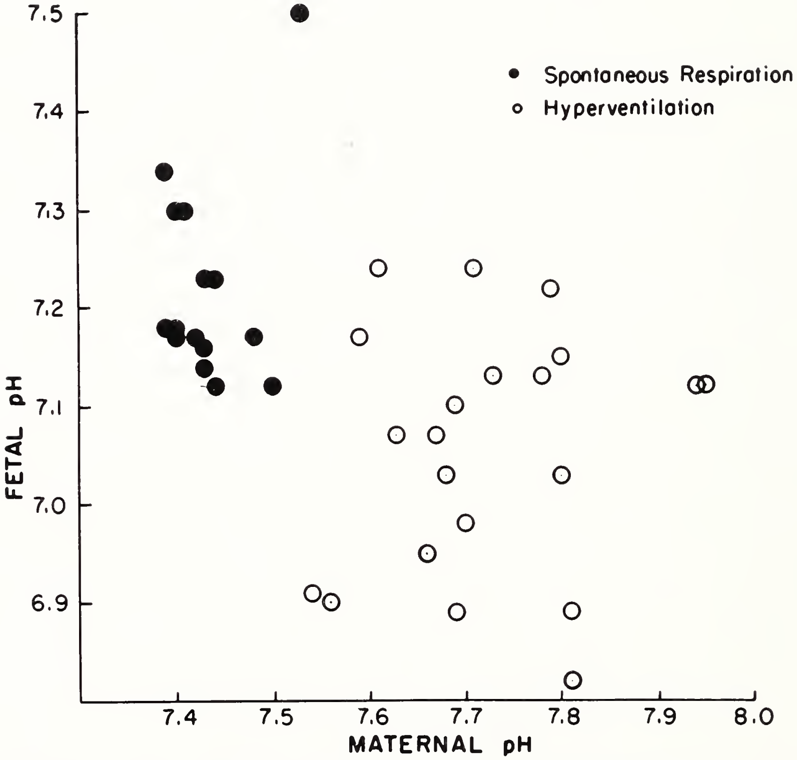

FIGURE 100.—The relationship between maternal and fetal pH. The pH of the umbilical vein blood is plotted against the pH of the maternal artery. Note fetal acidosis when maternal pH exceeds 7.5. Reprinted, by permission, from Morishima, H. O., Moya, F., Bossers, A. C., and Daniel, S. S.: Adverse effects of maternal hypocapnia on the newborn guinea pig. *Amer J Obstet Gynec 88: 524–529 (Feb 15) 1964* (The C. V. Mosby Co., St. Louis, publishers).

From our human data in nearly 80 mothers who were hyperventilated to various degrees, we were unable to show a correlation between maternal arterial pressure and pCO_2. Nevertheless, in the infants who were depressed at birth, there was not only a large pH gradient between umbilical vein and maternal arterial blood, but a reduced difference in oxygen saturation between the umbilical artery and vein blood; the oxygen level in both vessels was low and the arteriovenous difference was approximately 4 percent. This was indirect evidence that the uterine circulation had been reduced even though there had been no change in maternal arterial pressure. It emphasized that a normal maternal brachial artery pressure does not assure normal perfusion of the intervillous space.*

FREMONT-SMITH. Did you have any indication that the arterial pressure at the uterine level was influenced by the mother's hyperventilation, other than the fact that the babies were depressed?

JAMES. We didn't measure uterine blood pressure or flow.

COOK. What was the lactic acid concentration?

JAMES. The lactic-pyruvic ratio in the depressed infants was considerably higher.

SEGAL. There is a study on nonpregnant surgical patients which shows quite a marked increment of metabolic acidosis following induced hyperventilation under anesthesia.[3] This could have a quite close bearing on the results presented by Dr. James.

BRUNS. Well, you would expect that from muscular work in hyperventilation, wouldn't you?

SEGAL. Except that the work I quoted involved a passive hyperventilation resulting from respiratory assistance by the anesthetist.

JAMES. I would next like to consider some of the factors which must be taken into account in the study of the passage of drugs across the placenta when they are administered near the time of delivery. When Pentothal Sodium is given for the final stages of delivery, there has always been a question as to why a baby can cry lustily at birth (interpreted as awake) while the mother is deeply asleep. This cannot be explained on the basis of failure of the drug to cross the placenta, since relatively high concentrations (up to 13 mg/liter) are present in the umbilical vein. This has led some investigators to conclude that the fetus is less susceptible to the depressant effects of pentothal.

However, when blood from both the umbilical artery and vein is analyzed for barbiturate levels, we have found relatively low levels in the umbilical artery.[4] Furthermore, in all instances samples from the infant after birth have shown very low levels of the drug (fig. 101). These data suggest that

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**Editor's note.* This argument is further supported by Dr. Caldeyro-Barcia's data (p. 176).

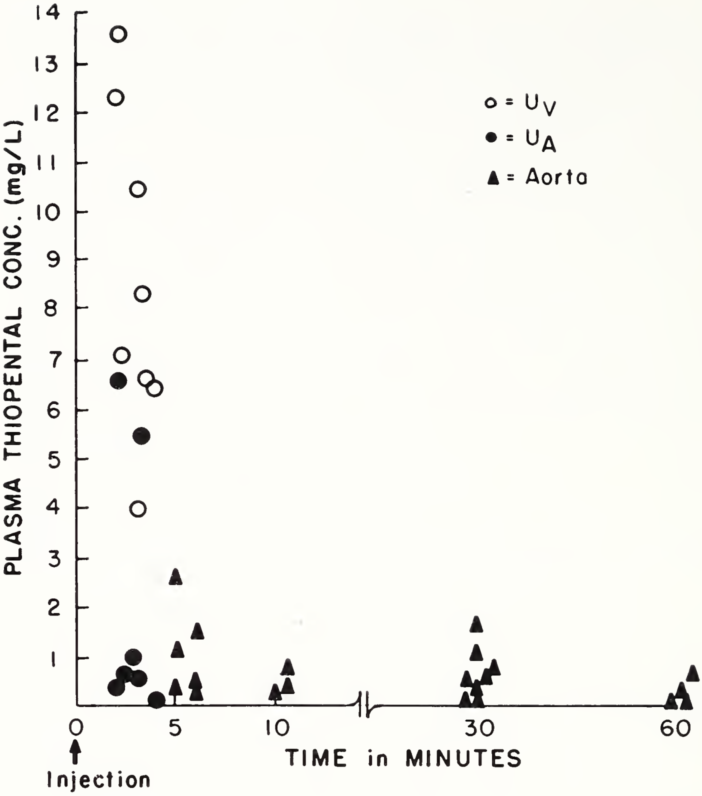

FIGURE 101.—Plasma thiopental levels in the umbilical vein and artery at birth and in serial arterial samples during the first hour of life.

if a drug which readily crosses the placenta is given to the mother during the final stages of delivery, very little of it will reach the infant's arterial blood and central nervous system. There are three possible explanations for this: compression of the umbilical cord, uptake of the drug by the liver before it reaches the systemic circulation, or serial dilution by several fetal streams.

BRUNS. Ploman and Persson [5] called attention to the higher concentration of barbiturates in the region of the fourth ventricle than in the cortex. Dr. James, do you believe that the barbiturates are concentrated in the brainstem of the baby?

JAMES. I don't think this occurs in the fetus, although it has been shown to occur in cats during severe hypercapnia.[6]

VILLEE. Should the difference between the concentrations in umbilical vein and artery be interpreted as the uptake of barbiturate by fetal tissues?

JAMES. That is one interpretation. However, you can only conclude this if you know that blood flow is unchanged. The wide arteriovenous difference, not only in drug concentration but also in pH, pCO_2 and O_2 saturation, indicates that interference in flow is the more likely explanation.

COMROE. Where is the interference with flow when it is already in the umbilical vein?

JAMES. To understand this, it is necessary to consider, in a dynamic way, the series of events which occur during delivery. When only the head has been delivered, the cord is compressed partly or completely. At this time, drug circulating in the intervillous space will cross into the fetal vessels at placental level. During the final stages of delivery (birth of lower body and feet) and immediately following, cord compression is no longer present and circulation through the cord becomes reestablished. Drug which has crossed the placenta during occlusion will then flow down the umbilical vein; blood from the infant flowing back to the placenta will contain little or no drug.

SEGAL. Couldn't this be a reflection of both a very slow blood flow which could get some barbiturate into the baby and a great deal of uptake, resulting in very little being reflected in the return to the placenta?

JAMES. Uptake by the fetal tissues, particularly the liver, is another explanation.

BRUNS. Could your differences be explained by protein binding?

JAMES. Protein binding is about the same in both infant and maternal blood. Uptake of pentothal by the fetal liver during prolonged administration to the mothers in whom the fetus was anencephalic has been studied by Baux and coworkers.[7] Drug concentration in the liver was more than four times higher than in muscle or subcutaneous fat.

CLEMENTS. Is the action of the barbiturate increased to any significant degree by change in pH?

JAMES. I think this is likely to be so. In asphyxiated individuals, a given dose of barbiturate will have a more depressing action.

CLEMENTS. I was wondering about the sequence of events in the baby after delivery. As he continues to correct his acid-base status, he might very well alter the effect of the anesthetic.

JAMES. He certainly might. However, these babies, though mildly asphyxiated, were born in a relatively lively condition and usually cried vigorously. Obviously, the amount of drug which had reached the central nervous system had not been sufficient to cause depression.

DAWES. Nevertheless, it may be relevant that the quantity of barbiturate in milligrams per kilogram required to anesthetize a newborn animal is about one-third to one-fifth that required to produce general anesthesia in an adult of the same species.

COOK. I also think that at least some experimental fetal animals are very sensitive to small doses of barbiturates given to the mother. The effect can be detected rapidly—within 1 to 2 minutes.

JAMES. I agree that the human fetus is likely to be more sensitive to barbiturates than is the adult.

Schafer. Is the time of drug administration in relation to delivery a factor? Do you see the same response in the infant if the drug is given 2 minutes or 1 hour before delivery?

James. I think there would be a difference. These data indicate that the central nervous system of the infant does not get very much drug. They don't reveal anything about placental transfer of drugs when maternal and fetal circulation are functioning normally. This was not our objective.

Bruns. Dr. Caldeyro has some data that might answer some of the questions you are posing.

UTERINE BLOOD FLOW DURING LABOR

Caldeyro-Barcia. The cardiovascular condition of the mother is a very important factor in uteroplacental circulation and fetal welfare.

Figure 102 illustrates the record obtained in a patient in whom systemic arterial hypotension was associated with Type II dips, perhaps because the occlusion of intramyometrial vessels by uterine contractions may occur more readily. During arterial hypotension (90/45 mm Hg) induced by the infusion of meperidine hydrochloride (Demerol) and chlorpromazine, uterine contractions are of relatively weak intensity, and Type II dips of

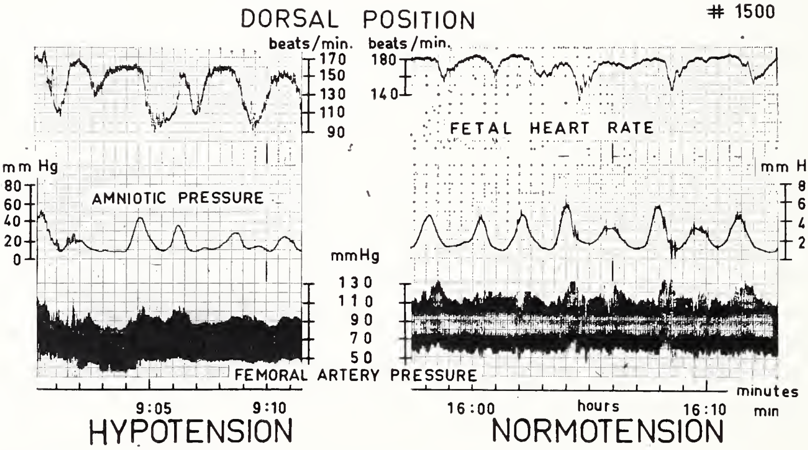

Figure 102.—*Left side:* Arterial hypotension facilitates the production of Type II dips of large amplitude. *Right side:* Seven hours later the arterial pressure has recovered normal levels, and the amplitude of Type II dips has greatly diminished. This record was obtained during labor induced with oxytocin infusion at full-term pregnancy. Reprinted, by permission, from Bieniarz, J., Fernández-Sepúlveda, R., and Caldeyro-Barcia, R.: Effects of maternal hypotension on the human fetus. *Amer J Obstet Gynec 92: 821–849 (July 15) 1965* (The C. V. Mosby Co., St. Louis, publishers).

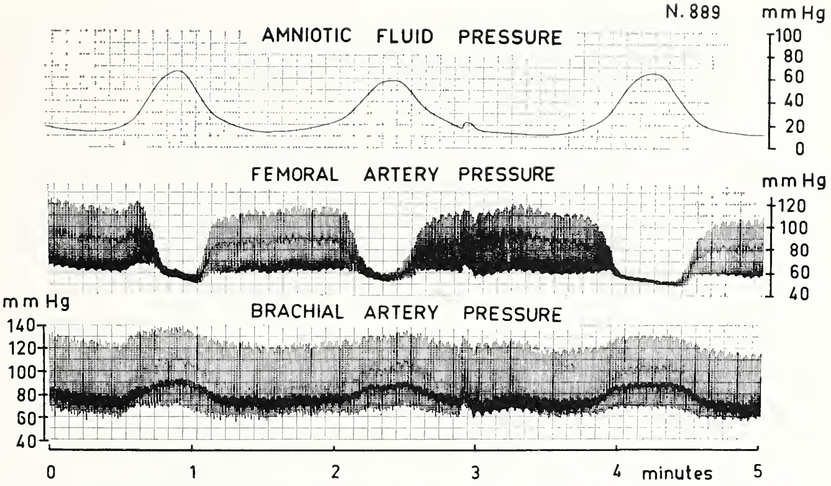

FIGURE 103.—Each uterine contraction caused a marked fall of arterial pressure in the femoral artery, with disappearance of pulse pressure. The systemic arterial pressure rose moderately during each uterine contraction, as shown by the tracing obtained from the brachial artery. Reprinted, by permission, from Poseiro, J. J., Bieniarz, J., Massi, G. B., and Caldeyro-Barcia, R.: Effects of uterine contractions of the pregnant human uterus on the aorta and iliac arteries. To be published.

very large amplitude and long duration are seen. After arterial pressure had recovered to its initial normal levels (115/55 mm Hg), the amplitude and duration of Type II dips diminished, despite the fact that uterine contractions were stronger than before.

It is important to record the blood pressure, not only in the brachial artery but also near the origin of the uterine artery during labor. In some pregnant women there may be a marked pressure difference between the two areas. When the parturient woman is in the supine position the contracting uterus may compress the terminal segment of the aorta or one common iliac artery against the spine. A record of arterial pressure obtained from the femoral artery during uterine contraction often shows a marked reduction of the amplitude of the pulse wave which may disappear completely (fig. 103). During uterine contraction, the mean arterial pressure in the femoral artery falls below the value of the diastolic pressure recorded when the uterus was relaxed. These effects of uterine contractions on the femoral arterial pressure are designated as the "Poseiro effect" since they were first observed by Dr. Juan J. Poseiro.

The record of arterial pressure obtained simultaneously from the brachial artery shows that in the upper half of the body, uterine contractions produce the usual rise of arterial pressure. The pressure fall recorded in the femoral artery is not a systemic effect but a local one. It is assumed that a similar fall occurs in the uterine arteries, since they originate from the arterial system distal to the area compressed by the uterus. This fall in blood pressure facilitates the compression by uterine contractions of the intramyometrial aspect of the vessels supplying the intervillous space.

RUDOLPH. Where and how was the pressure recorded?

CALDEYRO-BARCIA. A catheter was inserted into the femoral artery to the external iliac artery, and connected with a pressure transducer and a recording manometer. The same system was used for recording the brachial artery pressure and the amniotic pressure.

COMROE. Is the effect shown in figure 103 due just to uterine contraction or a uterine plus abdominal muscle contraction?

CALDEYRO-BARCIA. This was due solely to the contraction of the uterus. The woman was not bearing down, and the glottis was open.

RAMSEY. We have noted similar changes in pressure in monkeys. We have put a catheter into one femoral artery, low in the femoral triangle, and, in the other femoral artery, have threaded another catheter into the aorta above the takeoff of the renal, which was high enough that mechanical activity of the contracting uterus was not reflected.

Remembering that the monkey has a different kind of pelvis and a different kind of life habit, we have not been able to abolish this effect by changing the position of the animal. We have not found it in all animals. It is quite variable, as Dr. Caldeyro said. We have also found the opposite response, that is, an occasional rise in blood pressure with the uterine contraction.

SEGAL. Dr. Caldeyro's data showed a drop of femoral artery pressure during contraction. On the other hand, the syndrome which has been described in relation to the feeling of faintness in the supine position and the fall of maternal blood pressure is related to the relaxation of the uterus, when this gravid organ may fall back upon the inferior vena cava.

CALDEYRO-BARCIA. You are describing the so-called "supine hypotensive syndrome." It is well known but an entirely different situation from that illustrated in figure 103. My purpose is to emphasize that one cannot assume that the blood in the uterine artery is the same as measured by a cuff around the brachial artery. The difference is slight when the uterus is relaxed, but it may become great when the uterus contracts. The compression exerted by the contracting uterus on the aorta is much higher than the pressure exerted on the amniotic cavity. Figure 103 shows that uterine contractions which cause rises of intrauterine pressure up to 60 mm Hg are able to occlude the aorta or the common iliac artery, which have a systolic pressure of 120 mm Hg and a diastolic of 60 mm Hg. The occlusion is obtained before the contraction reaches its peak.

BRUNS. Dr. Caldeyro, is this a mechanical phenomenon?

CALDEYRO-BARCIA. Yes, it is purely mechanical. Compression occurs above the bifurcation of the aorta and below the renal arteries (fig. 104).[8]

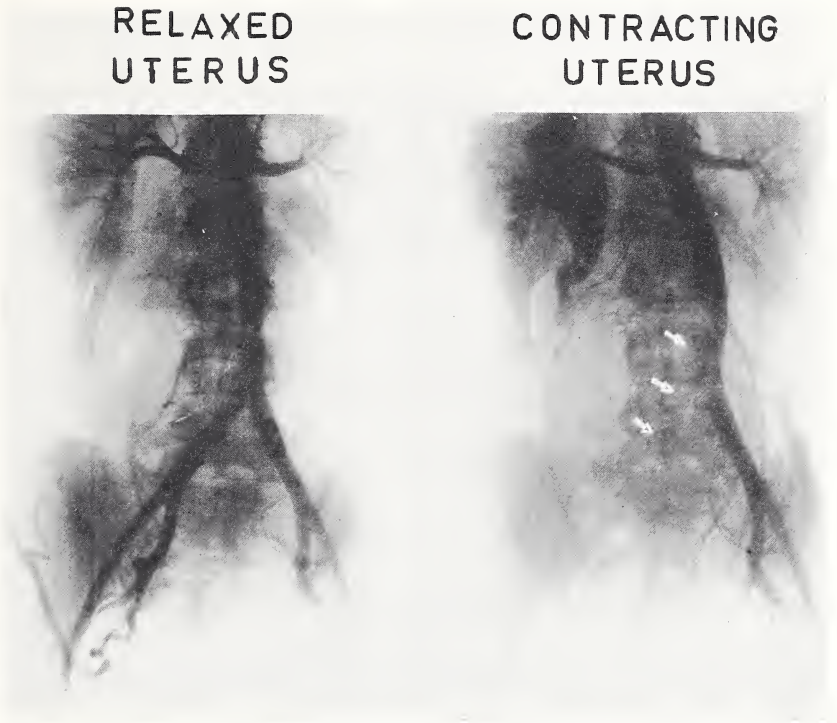

Figure 104.—The contracting uterus compresses the lower aorta and the right common iliac artery. Radiographs were taken after injection of contrast medium into the abdominal aorta, 2 seconds after injection on the left radiograph, and 4 seconds after injection on the right. Mother in supine position. On the left, the injection was made when the uterus was relaxed (amniotic pressure 10 mm Hg). On the right, the uterus was contracting, the amniotic pressure was rising and had reached 50 mm Hg at the moment of the injection. With relaxed uterus the contrast medium filled the abdominal aorta and bilaterally the renal arteries, the common iliac artery and their branches. The contracting uterus displaced the lower abdominal aorta toward the left, reduced its lumen (at L IV) and prevented the filling of the right common iliac artery and all its branches, including the uterine artery. Subsequent films of each series showed good filling of intervillous space with the relaxed uterus and no filling with the contracted uterus. Reprinted, by permission, from Bieniarz, J., et al: Compression exerted by the contracting pregnant human uterus on the lower abdominal aorta and its branches. To be published.

Dawes. Are you sure that the tip of the catheter is not being blocked by a shift in position? In animals, transient movements can cause spurious records.

Caldeyro-Barcia. No, this is not a recording artifact. In these women, the arterial pulse in the *dorsalis pedis* artery disappears during uterine contraction. This effect can be observed in about 15 percent of parturient women when they lie in the supine position.

Figure 105 illustrates how the fall of maternal arterial pressure facilitates the production of Type II dips, when all the other factors remain constant. The record was obtained in a term pregnant woman with severe preeclampsia (arterial pressure 170/100 mm Hg) in which strong uterine contractions produced Type II dips of small amplitude; the "Poseiro effects" are not present. The intravenous infusion of Demerol and chlorpromazine caused a progressive drop of arterial pressure to 100/60 mm Hg. At this pressure level, most of the uterine contractions caused a clear "Poseiro effect" on the record of the femoral arterial pressure. The simplest explanation of this change is that the uterus compresses the aorta more easily when the intraaortic pressure has diminished.[9] The woman remained in the supine position at all times. Following the fall of arterial pressure, there was a marked increase in the amplitude of Type II dips.

Cross. At hour 5:02, there is a considerable slowing of the fetal heart, but no effect on the mother's pressure?

Caldeyro-Barcia. Correct. After hour 5:02, the Type II dips have a much greater amplitude because of the fall in systemic pressure which acts through two mechanisms: (1) It reduces the head of pressure perfusing the uteroplacental vessels and facilitates the occlusion of the intramyometrial part of the vessels by uterine contractions; (2) it facilitates the compression of the aorta or the common iliac artery by the contracting uterus, which will further reduce the pressure in the uterine artery.

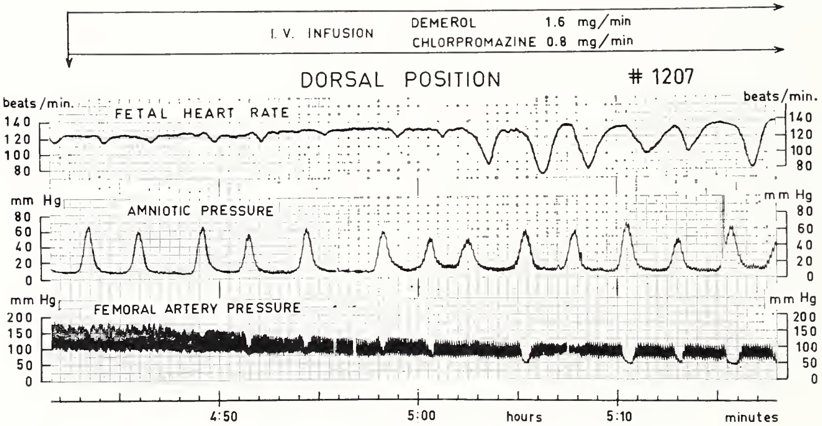

Figure 105.—The effect of changes in maternal arterial pressure on the "Poseiro effect" and in the production of Type II dips. Record obtained during labor in a severe preeclampsia. Cervical dilatation 3 cm. Intact membranes. (See text for details.) Reprinted, by permission, from Bieniarz, J., Fernández-Sepúlveda, R., and Caldeyro-Barcia, R.: Effects of maternal hypotension on the human fetus. *Amer J Obstet Gynec 92: 821–849 (July 15)1965* (The C. V. Mosby Co., St. Louis, publishers).

Rudolph. It also appears to be variable in the same individual, because in the contraction occurring at about 5:08 there was no significant effect on arterial pressure.

Caldeyro-Barcia. The successive uterine contractions in the same woman do not necessarily have the same pattern. They may start in different areas of the uterus (see fig. 25, p. 34) and spread in different directions. The way in which they compress the aorta or the iliac arteries may differ. Despite this fact, the contraction did have a clear effect on the fetal heart rate.

A remarkable demonstration of the consequences of the "Poseiro effect" on fetal heart rate is shown in figure 106. This record is a continuation of that illustrated in figure 105. In the supine position, uterine contractions cause a marked "Poseiro effect" and Type II dips of large amplitude. When the patient changes to the lateral position and the contracting uterus no longer compresses the aorta or iliac artery, the "Poseiro effect" disappears and the amplitude of the dips is greatly reduced.

When the infusion of Demerol and chlorpromazine is discontinued, the arterial pressure progressively recovers (fig. 107). It takes approximately 6 hours to reach its initial values. Figure 107 shows four parts of the tracing corresponding to this phase of recovery. As the arterial pressure returns to initial hypertensive values, the "Poseiro effect" as well as the Type II dips diminish in amplitude and finally disappear, despite the fact that the intensity of the uterine contractions is not altered.

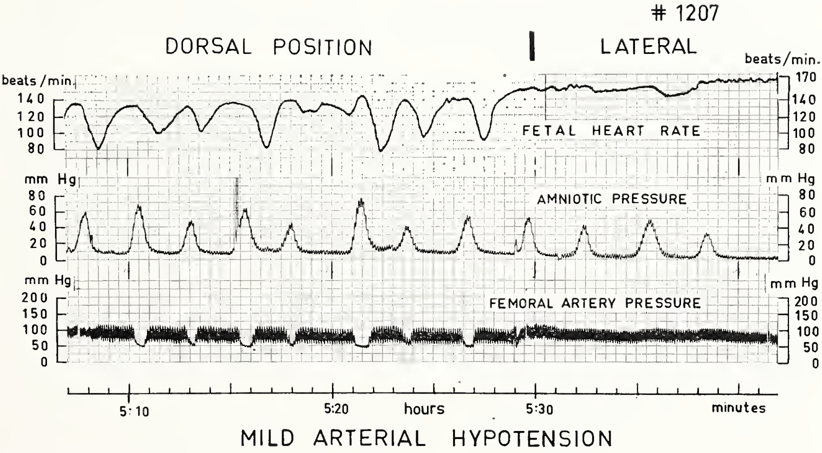

Figure 106.—Continuation of figure 105. Reprinted, by permission, from Bieniarz, J., Fernández-Sepúlveda, R., and Caldeyro-Barcia, R.: Effects of maternal hypotension on the human fetus. To be published.

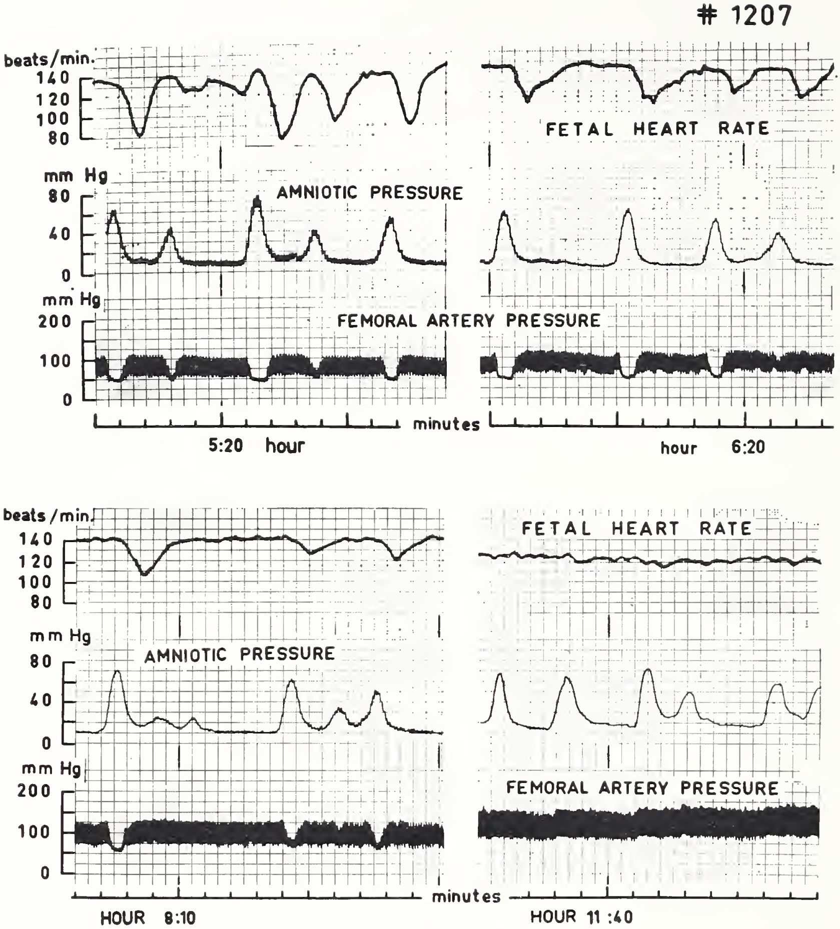

Figure 107.—Continuation of the record illustrated in figures 105 and 106. Mother in supine position during the four segments of record illustrated here. Reprinted, by permission, from Bieniarz, J., Fernández-Sepúlveda, R., and Caldeyro-Barcia, R.: Effects of maternal hypotension on the human fetus. *Amer J Obstet Gynec 92: 821–849 (July 15) 1965* (The C. V. Mosby Co., St. Louis, publishers).

Smith. How does a woman like to lie when she is in labor? Does she prefer to lie on her back or on her side? Are women aware of the sudden changes in blood pressure?

Caldeyro-Barcia. If I would have to be delivered again, I would like my mother to be standing.

Alway. Is there relevance to the primitive practices of squatting?

Caldeyro-Barcia. I think it is a much better position than lying down.

Comroe. Dr. Smith, a normal individual can compress the abdominal aorta easily by strong contraction of the abdominal muscles. I am sure people who do that, do it many times during their lives and don't have any symptoms resulting from it.

RUDOLPH. I wonder if the drop in femoral artery pressure could be explained by compression of the external iliac arteries where they cross the brim of the pelvis, rather than on the basis of compression of the abdominal aorta. If the head of the baby is engaged in the pelvis, uterine compression could force a fairly firm structure against the arteries at the pelvic brim.

FREMONT-SMITH. Is your catheter above the iliac arteries?

CALDEYRO-BARCIA. In some cases, in which we put in three catheters, the compression is above the aortic bifurcation. In others, the compression appears to be at the iliac artery.

CRYING VITAL CAPACITY IN INFANTS BORN BY CESAREAN SECTION

SEGAL. These studies were carried out in collaboration with Dr. Josephine Chu.[10]*

In an attempt to learn more about the pathogenesis of the respiratory distress syndrome, we chose to study the possible effects of cesarean section, in order to eliminate the etiologic factors relating to prematurity. In our local experience over a 5-year period, excluding the infants of diabetic mothers, we did not encounter this syndrome beyond the premature weight group, unless cesarean delivery had been involved.

To avoid emergent maternal and fetal factors which could have compromised the infant, these studies were carried out on elective section deliveries and also on a control group of infants delivered vaginally. The only selection pertaining to these two groups of term infants was to choose a convenient time of day.

From these original groups, we excluded a number of babies whose delivery had followed a definite sign of predelivery period of distress, as judged by slowing of the fetal heart rate. We excluded studies in instances of recognized maternal disease and also those with neonatal respiratory distress lasting over 4 hours.

After these exclusions, we were left with 26 pelvic and 36 cesarean deliveries, with a mean birth weight of 3.4 kg and 3.3 kg, respectively, and a mean gestational age of 40.2 and 39.2 weeks, respectively. The clinical condition of these two groups of babies at birth, as documented by their Apgar score, was quite comparable.

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*These investigations were supported by National Health Grants, Canada, 609–13–23.

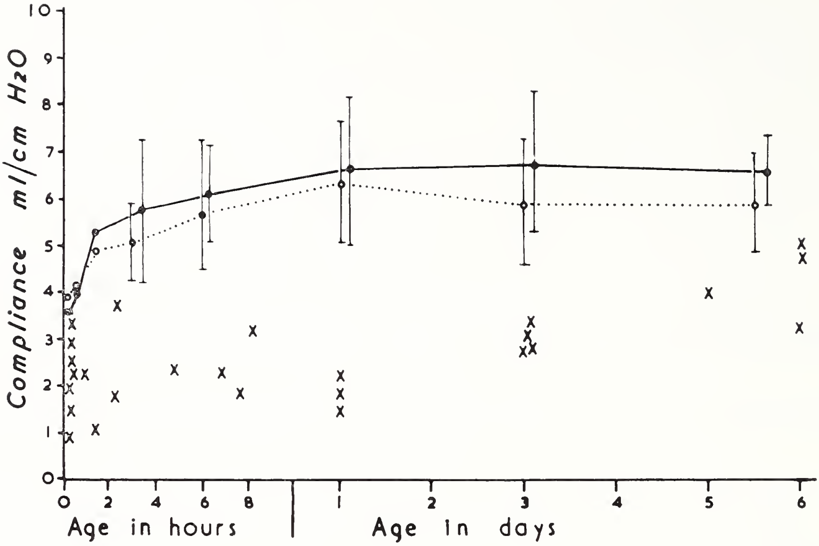

FIGURE 108.—Mean compliance according to age, showing $\overset{\top}{\underset{\bot}{\circ}}$ $\overset{\top}{\underset{\bot}{\bullet}}$ SD. ●——● = vaginal delivery; ○——○ = cesarean section; X = individual infant with distress.

We measured their crying vital capacity with a reverse plethysmograph.[11] The crying vital capacity was the greatest volume that a baby produced in response to a sharp slap on the foot. The stimulus was repeated 5 to 10 times on each of the babies.

The results obtained within a few minutes after birth, and at systematically designated intervals thereafter, showed a smaller crying vital capacity in the babies who had been delivered by cesarean section, and this difference persisted during the full 6 days of the baby's stay in the nursery (fig. 108). The data marked by X's, which were from babies with respiratory distress, were excluded from the calculations.

Because of the differences of birth weight between these two groups, the crying vital capacities have been related to body weight (table 2). The values shown are the means for each of the age groups.

This could mean that the babies were unable to cry as vigorously if they were delivered by cesarean section. If this has any physiological meaning, an explanation for it must satisfy the observations that this difference persisted for the whole of the 6-day period.

AVERY. How reproducible is a measurement in a given baby, within an hour or so?

SEGAL. It is quite reproducible.

SMITH. One is troubled about the fact that the difference is greatly reduced when you calculate it according to birth weight, and by the question of what it might be in cesarean section that might have a lasting effect

Table 2.—*Crying vital capacity equated to birth weight: comparison of infants delivered vaginally and by cesarean section for each age period*

Age	Vaginal		Cesarean		Difference ml/kg	Level of significance
	cVc ml/kg	Number of studies	cVc ml/kg	Number of studies		
2 to 10 min	25.2	4	23.4	23	4.7	*<.01
11 to 60 min	29.7	22	25.3	22		
1 hr 1 min to 2 hr	31.5	16	27.1	16	4.4	<.05
2 hr 1 min to 4 hr	31.7	9	27.7	10	4.0	>.05
4 hr 1 min to 8 hr	31.4	26	27.9	34	3.5	<.01
1 to 5 days	34.7	58	31.0	84	3.5	<.001
6 days	37.1	10	32.7	23	4.4	<.01
Mean, all ages	32.5	145	28.5	212	4.0	<.001

*Age groups 2 to 10 min and 11 to 60 min combined.

on the baby, besides being delivered through the abdominal wall. I suppose the anesthesia and analgesia were not the same with these elective sections?

Segal. All of these were elective sections, elected because of previous cephalopelvic disproportion. The anesthesia in the two groups did differ in that almost all of the pelvic delivery patients received inhalation anesthesia consisting of nitrous oxide or nitrous and cyclopropane, or just cyclopropane, and almost all of the sections were performed with spinal anesthesia.

Smith. It is important to have this worked out, because this is the only piece of information I know of that has shown differences in the baby delivered by cesarean section and the baby delivered vaginally.

Segal. Of course, the crying vital capacity is a very crude measurement, but perhaps it is not much more crude than vital capacity in the adult. It may be affected by nonpulmonary factors.

Klaus. The functional residual capacity (lung volume at end expiration) in infants delivered vaginally and those delivered by elective cesarean section are similar by 30 minutes of age.

Oliver. Other differences between vaginally delivered babies and those born by elective cesarean section have also been observed.[12] These include differences in acid-base balance, protein concentration, and hematocrit. Differences in the former disappear within the first hour of life. I don't know how long the differences in protein and hematocrit persist.

Fremont-Smith. In what way are they different?

OLIVER. The cesarean section babies had lower serum proteins and hematocrits and were more acidotic.

SEGAL. There are a number of other differences. Cornblath has shown differences in their response to glucagon; lower serum calcium and higher potassium have been reported as compared to vaginal delivery.

VILLEE. Would you elaborate a bit on the difference in the glucagon tolerance test and what explanation there is for this difference?

OLIVER. The glycemic response to small amounts of glucagon (30 μg/kg) of infants born after cesarean section without labor was much less than the response of infants delivered vaginally. This difference was obliterated if there was labor before the cesarean section.[13]

VILLEE. How do you interpret this?

OLIVER. Cornblath suggested it might be related to the known increased production of 17-hydroxy-corticosteroids which occur after a trial labor, whether subsequent delivery is by cesarean section or vaginally.

COOK. Dr. Segal, have you definitely shown a difference in vital capacity in these two groups? An important fact may well be that these babies were 7 days different in their gestational ages. Perhaps the more immature infants born by section might have had the same vital capacity by the time they reached the age of the vaginally delivered group. You have only shown that cesarean section babies have less muscle strength and/or a lower lung compliance which may, indeed, both be physiologic for their age.

SEGAL. At 6 days of age the differences are still there.

COOK. The performance at 6 days of the cesarean section group is as good as the newborn of the noncesarean section group, is it not?

SEGAL. I don't think the results for the first 24 hours should be considered here because there is a tremendous increase in both during this period. I think you have to start from day 1 in the comparisons.

AVERY. Those little X's in the figure interest me much more than the two lines. Were those babies subsequently proved to have something we accept as hyaline-membrane disease?

SEGAL. There were no deaths in our series. If we include the X's, this would make the differences very much more impressive, because this would bring the averages down for the cesarean sections. There were six cesarean section babies and one vaginal delivery in that group with overt respiratory distress who would have been expected to show the classical membranes, had they not survived.

AVERY. Why didn't you include these babies?

SEGAL. We didn't include them because they had respiratory distress and we wanted to see whether clinically normal infants delivered by elective section would show differences. If they did, this would be an objective piece of evidence to suggest that this particular method of delivery places the infant at a physiological disadvantage.

Comroe. Didn't you relate the vital capacity to height or stem height?

Segal. Yes, we have regression equations relating the measurements to stem length, chest circumference, and body weight. These were derived from vital capacity determinations during the period from 1 to 6 days, omitting the interval of rapid change during the first 24 hours. The difference in crying vital capacity persists when we use these parameters.

Karlberg. Was the cord clamped later in the vaginal deliveries?

Segal. There were a number of people who did these deliveries, and the range of differences of technique was quite broad.

Bruns. How do you determine your duration of gestation?

Segal. These were done by the obstetrician. All we can say is that there is bound to be a systematic gestational difference between babies born at term, spontaneously, and those born by elective section, when the obstetrician is trying to avert a trial of labor and possibly a vaginal delivery. I should add that none of these studies has been carried out on babies whose mothers had gone into labor before the cesarean section had been performed. I believe there is a great need for doing this.

Levine. Were there any sex differences or gravidic differences in the two groups?

Segal. The gravidic differences have not yet been analyzed. There were sex differences, with more females in the cesarean section group.

James. What about the respiratory rates? Were they higher in the cesarean section group?

Segal. Yes, and this has been documented by others.[14]

Smith. How much could the squeeze of putting the baby through the birth canal have to do with Dr. Segal's data?

Karlberg. By means of X-ray, Borell and Fernström [15] have shown that there is compression of the thoracic cage during vaginal delivery. Such a squeeze must facilitate drainage of the amniotic fluids from the respiratory tract which is in keeping with the clinical experience that fluid is expelled when the head is delivered and the thorax is still in the birth canal. Since there is an elastic recoil of the thorax immediately after the complete delivery, the magnitude of the squeezing effect may be evaluated from recorded inspiratory volume changes during this recoil. We have found great variations, from 0 ml to 50 ml.[16]

Since there seems to be an inverse relationship between this inspiratory volume change and the residual volume from the first breath, there is difficulty in assessing the effect of the squeeze on the further development of the vital capacity.

Oliver. Haven't you observed differences in the pressure volume diagrams of the first breath, if a large volume occurred during the squeeze and recoil as compared to a small one?

Karlberg. These findings belong to another study [17] not combined with recording of the effect of squeeze. However, there appears to be a relationship.

LUNG COMPLIANCE AND LUNG VOLUME

Klaus. These studies are an extension of the work of Dr. Karlberg,[18] who has shown that lung compliance increases remarkably during the first day of life. We were interested in knowing whether this increase was secondary to changes in lung volume. We measured tidal volume and lung volume with a body plethysmograph, and intrathoracic pressure with an airfilled balloon in the esophagus. Lung volume was measured before and after each determination of compliance. Figure 109 shows the lung compliance and func-

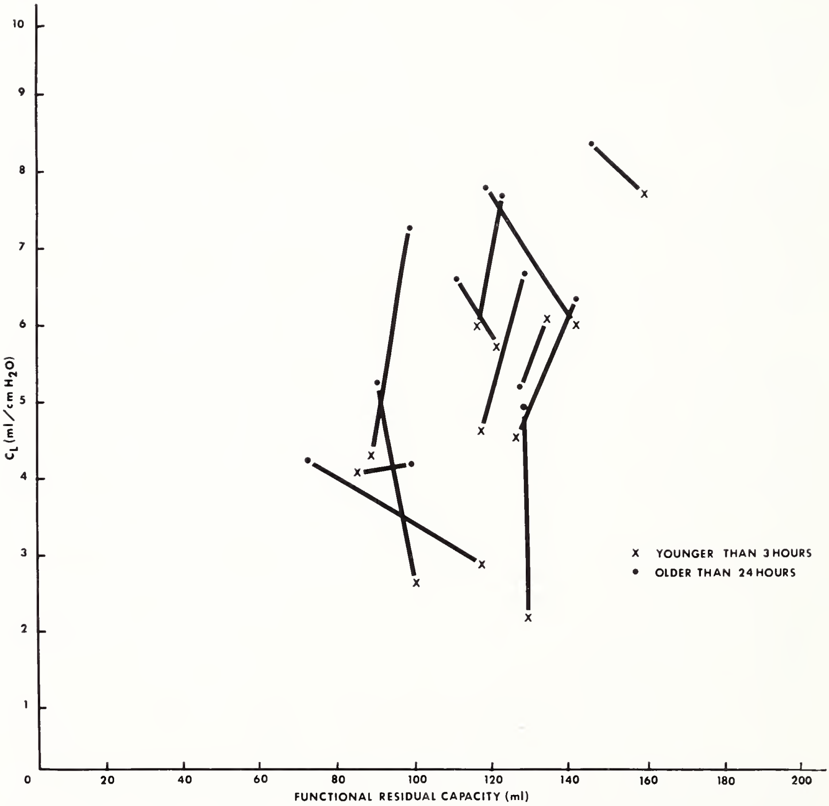

Figure 109—Lung compliance and functional residual capacity in 12 infants before 3 hours and after 24 hours of age. Reprinted, by permission, from Chu, J. S., Dawson, P., Klaus, M., and Sweet, A. Y.: Lung compliance and lung volume measured concurrently in normal full-term and premature infants. *Pediatrics 34: 525–532 (Oct) 1964.*

TABLE 3.—*The lung compliance and functional residual capacity in full-term infants at different ages*

	Number of infants	Number of studies	Compliance/kg of body weight (ml/cm H_2O/kg)	Functional residual capacity/kg of body weight (ml/kg)	Compliance/functional residual capacity (ml/cm H_2O/ml)
Full-term infants younger than 3 hours	17	17	1.5±0.5	36.6±7.5	0.04±0.010
Full-term infants older than 8 hours	31	32	2.0±0.4	38 ±5.2	0.053±0.0094
Significance of difference			$P=0.001$	Not significant	$P<0.001$

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tional residual capacity (FRC) in 12 infants before 3 hours of age and again after 24 hours of age. In the majority of infants, there is a marked increase in compliance with very little change in lung volume. Table 3 shows this in a larger number of infants. The lung volume did not change significantly, but compliance increased from 1.5 ml/cm/kg to 2.0 ml/cm/kg; and specific compliance increased from 0.04 to 0.053 ml/cm H_2O/ml.

SMITH. What is "specific compliance"?

KLAUS. Specific compliance is the lung compliance divided by the lung volume. The increase in lung compliance could be secondary to the same volume being distributed among a larger number of units, a change in the elasticity of the lung tissue, or possibly some change in the alveolar surface tension.

KARLBERG. Do you use the actual weight or the birth weight?

KLAUS. Since there was very little change in the time, we used birth weight. While collecting these measurements, we also observed interesting differences in FRC in relation to birth weight. Table 4 shows the FRC at different birth weights. The FRC/kg decreases from 51 ml/kg in the 1,000 to 1,500 gm range to 29 ml/kg at 4,000 gm. The small premature infant may compensate for narrow airways by increasing its FRC. This would increase airway size slightly and therefore lower airway resistance. If the FRC is related to the expected lung weight, using Gruenwald's [19] autopsy data it can be seen that there is a constant ratio of FRC/gm of lung.

TABLE 4.—*Functional residual capacity in relation to birth weight and expected lung weight*

Birth weight (kg)	Number of infants	Functional residual capacity (ml)		
		Total	Per kg of body weight	Per gm of expected lung weight*
1.01 to 1.50	5	82	51. 1	2. 2
1.51 to 2.00	13	98	49. 4	2. 3
2.01 to 2.50	11	95	45. 0	2. 1
2.51 to 3.00	16	115	41. 7	2. 4
3.01 to 3.50	7	108	34. 2	2. 1
3.51 to 4.00	6	119	31. 0	2. 3
4.01 to 4.50	2	123	29. 2	2. 3

*Calculated from the data of Gruenwald and Minh.

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POTTER. When a baby weighs as much as 4,000 gm, it has an excessive amount of fat without any actual great increase in organ size or lung volume. Thus, beyond 3,000 gm you would expect the decrease.

COOK. In line with Dr. Potter's comment, it would be interesting to relate the FRC to the crown-rump length or total length, because it has frequently been shown that lung volumes are much more closely related to a linear length than they are to body weight.

DAWES. What is the normal relationship between lung weight and body weight at different gestational ages in man? In the sheep, at earlier gestational ages, the lung is a greater proportion of total body weight than it is at term.

POTTER. That is also true in the human infant. In my experience, if you compare the organs of infants and fetuses with a birth weight of 1,000 to 1,500 gm with those of 4,000 to 4,500 gm, all organs weigh proportionately more in the first than they do in the second group.[20]

DAWES. Could the differences you have just described possibly be due to changes in interstitial fluid content in the lung? What happens to pulmonary lymph flow, for instance, when the lung is first ventilated? In the unventilated lung of the fetus, is there an excessive amount of fluid in the lung substance which has to be gotten rid of during the first 24 hours or, perhaps, longer after birth?

KLAUS. I don't think we know anything about the pulmonary lymph flow. Dr. Avery can tell us about the fluid lost during the first day of life.

AVERY. Fetal lungs are relatively wetter.

DAWES. Granted, everyone will agree they are relatively wetter, but where is the fluid?

AVERY. When you take sections, it appears to be in the air spaces. This is crude. I can't answer whether tissue levels are higher.

COOK. Severe pulmonary edema represents an increase in lung weight of only 10 percent. It would be difficult to measure minor changes in interstitial fluid.

DAWES. But the splinting effect on gaseous expansion of the lung might be very considerable.

JAMES. How about increased blood flow through the ductus? Changes in left atrial pressure, which we have measured over the first few hours of life, parallel your changes in compliance.[21] We have interpreted the higher left atrial pressure during the first 3 hours of life as probably reflecting increased left-to-right flow through the ductus at this time. The high V waves would also support this.

KLAUS. One must increase the blood volume in the lung markedly to change lung compliance.

KARLBERG. We have found a similar correlation of FRC to weight.[22] I agree with Dr. Cook that height correlates better.[23] I do not like to use calculated surface area for several reasons, one of which is that the Du Bois' height-weight formula was not based on newborn nor premature infants. The youngest test subject was a 21-month-old, poorly nourished girl with a weight of 6.27 kg.[24] Have you noticed any change in the FRC after the third day, Dr. Klaus?

KLAUS. We found it was fairly constant from 20 minutes to 5 days of age.

KARLBERG. Dr. Smith, didn't you find variations in the FRC during the first week?

SMITH. We found very little change.

ALVEOLAR-ARTERIAL OXYGEN GRADIENT

SMITH. Drs. L. S. Prod'hom, Nicholas Nelson, Henry Levison and Miss Ruth Cherry in our laboratory have gathered data on the oxygen gradient from alveolus to arterial blood. Dr. Gairdner in Cambridge has done work with much the same findings.[25] In 19 babies the mean alveolar-arterial Po_2 gradient was 27 mm Hg in the normal baby of 6 to 74 hours (table 5). This value is about three times that of the normal adult. The reason for this is the lower arterial oxygen tension of the newborn, as measured from a catheter in the umbilical artery.

TABLE 5.—*Oxygen and carbon dioxide pressure gradients between alveolar air (A) and arterial blood (a)*

	Normal adult (mm Hg)	Normal newborn infant (mm Hg)
$P_{A_{O_2}}$	104	107. 0± 6. 3
$P_{a_{O_2}}$	95	79. 3± 10. 4
[A–a] P_{O_2} gradient	9	27. 2± 9. 6
$P_{A_{CO_2}}$	38–40	32. 7± 4. 0
$P_{a_{CO_2}}$	40	34. 8± 6. 5
[a–A] P_{CO_2} gradient	0–2	1. 9± 4. 0
	n=19 BW=1.70–3.74 kg age=6h–74h	

Table compiled from data in Nelson, N. M., et al: Pulmonary function in the newborn infant: The alveolar-arterial oxygen gradient. *J Appl Physiol 18: 534, 1963* (for normal newborn infants, oxygen); and Nelson, N. M., et al: Pulmonary function in the newborn infant: II. Perfusion—estimation by analysis of the arterial-alveolar carbon dioxide difference. *Pediatrics 30: 975, 1962* (for normal newborn infants, carbon dioxide).

STAHLMAN. Was the catheter above or below the ductus?

SMITH. Both places have been tried, but the catheter was usually below the ductus. In analyzing the contributions of the factors which may contribute to such a gradient, the factor of diffusion disturbances seemed, from a relatively few measurements, to be no more significant than in the normal adult (table 6). When the so-called virtual shunt or the venous admixture from so-called virtual shunts was removed by giving the infant 100 percent oxygen to breathe, so that the factors of diffusion and distribution were removed, essentially all of the 27 mm Hg gradient was shown to be due to true right-to-left shunting, as most of the 9 mm gradient is in the adult. The gradient was greater at 20 minutes and took 2 or more days to come down to the range of 27 mm Hg (table 7). The calculation of true shunt cannot be done at 20 minutes, because the test requires that the baby breathe oxygen for half an hour. But the venous admixture, calculated from all shunts, is about 37 percent of cardiac output.

COMROE. Why does it require a half hour?

SMITH. That is what the respiratory physiologists tell us.

TABLE 6.—*Components of alveolar-arterial oxygen tension gradients in normal adults and newborn infants*

Components of gradient	Normal adult (mm Hg)	Normal newborn infant (mm Hg)
Diffusion	0–1	0–1
Distribution	variable	0
Shunt	2–4	27
Total gradient	9–10	27

Reprinted, by permission, from Smith, C. A.: Respiratory physiology and respiratory distress in the newborn infant. *Int Anesth Clin 3: 209–224 (Feb) 1965.*

COMROE. That may be true in people with very severe emphysema, but it should not be true in a hyperventilating infant, unless there is abnormal distribution.

SMITH. We have been sufficiently concerned over giving newborn babies so much oxygen to breathe that we have cut the time in some later ones to 15 minutes or so. I am glad you raised this question, because we would rather not give oxygen for such a long period.

It appears that the venous admixture is related largely to true right-to-left shunt. By true right-to-left shunt, we mean one which may be intrapulmonary, through the bronchial vessels or through vessels perfusing nonventilated areas of lung, or extrapulmonary, such as the normal one through the thebesian veins or the abnormal ones through the ductus arteriosus and through the foramen ovale. In a few simultaneous measurements of blood

TABLE 7.—*Changes in alveolar-arterial oxygen tensions, calculated venous admixture, and percentage of true right-to-left shunts at consecutive ages after birth*

Age	Number of infants	$P_{a_{O_2}}$ mm Hg	$P_{A_{O_2}}$ mm Hg	$P_{A_{O_2}}-P_{a_{O_2}}$ mm Hg	Venous admixture (percent)	True R–L shunts (percent)
20 minutes	13	55±8	101±8	47±6	37±9	....
1 hour	15	58±12	98±9	40±15	33±14	24±4
4 hours	12	68±9	102±7	34±12	23±9	22±5
24 hours	15	70±8	107±8	37±7	20±6	24±4
2–4 days	20	82±12	108±12	26±11	13±7	....
Adults	....	95	104	10	7	2–4

Table compiled from data in Prod'hom, L. S., et al: Adjustment of ventilation, intrapulmonary gas exchange and acid-base balance during the first day of life. *Pediatrics 33: 682, 1964.*

from above and below the ductus a right-to-left shunt through the ductus has not seemed to be a factor. We need more measurements, however. We don't know whether the foramen ovale is a factor.

Our group then studied a series of infants with respiratory distress. Babies who were distressed and breathing fast, who may or may not have been grunting but who were cyanotic outside of oxygen before 4 hours of age, were included.

The distressed infants fell into two groups. One type (there were nine at the time table 8 was made, and their pattern has been followed by additional babies studied subsequently) had a rather large shunt at 4 hours, which was larger at 12 hours, and still larger at 24 hours.

Dawes. Are the shunt figures the percentage of cardiac output which is shunted?

Smith. Yes. In so-called Type I infants FRC was slightly decreased at 4 hours and further decreased at 24 hours. Arterial pH was low. Ventilation was obviously not good, and there was an excess of acid in the blood.

Data from the other type of baby, whom we called Type II, were quite different. They had shunts which were relatively no bigger than those of the normal babies and did not particularly increase. Remember that "shunt" is used without definition of location and could be through or around the lungs, or both.

Table 8.—*Comparison of certain measurements from nine infants with respiratory distress of Type I (presumably atelectasis and hyaline membranes) and seven infants with Type II (presumably associated with aspiration)*

	Type I, hyaline membrane			Type II, aspiration		
	Age in hours			Age in hours		
	4	12	24	4	12	24
Shunt percent	*45	*60	*>65	*27	*28	*32
FRC	Sl. ↓	....	↓	N ↑	N	N
pH	7. 17	*7. 19	....	7. 20	*7. 30	7. 30
pCO_2	63	*57	*60	56	*44	*42
+Acid	4. 4	*5. 5	....	3. 2	*2. 7	3. 5

* Significant.

Reprinted, by permission, from Smith, C. A.: Respiratory physiology and respiratory distress in the newborn infant. *Int Anesth Clin 3: 209–224 (Feb) 1965.*

The relatively normal or even more than normal FRC (as though there might be some trapping of air in some sort of communication with the airways), the more normal arterial pH, better ventilation, and less acid accumulation of these infants is also noteworthy.

Most of the Type I babies died, and seven of the nine who did had hyaline membranes. The other two had very marked atelectasis without membranes. The babies listed as Type II survived. They may have been merely milder examples of Type I. By the helpful but inconclusive evidence of X-ray and by other clinical evidences, we decided that their respiratory distress was more likely to have been caused by aspiration of amniotic sac contents.

COMROE. When you say "aspiration," do you mean aspiration of materials which don't plug airways?

SMITH. I mean the sort of thing that can be seen in roentgenograms as big patchy areas which clear rapidly. Only in a few did the X-ray reveal the typical fine "reticulogranularity" so likely to be associated with hyaline membranes if the baby dies.

AVERY. How many of the Type II infants were premature?

SMITH. About half.

In addition to the factor of progressive hypoxia, which expresses itself as though there were a shunt in the infants with the hyaline membrane or Type I picture, there is a progressive acidosis (fig. 110). Beginning at 4 hours, the right-to-left shunt was 50 percent, and it rose to 90 percent at 74 hours

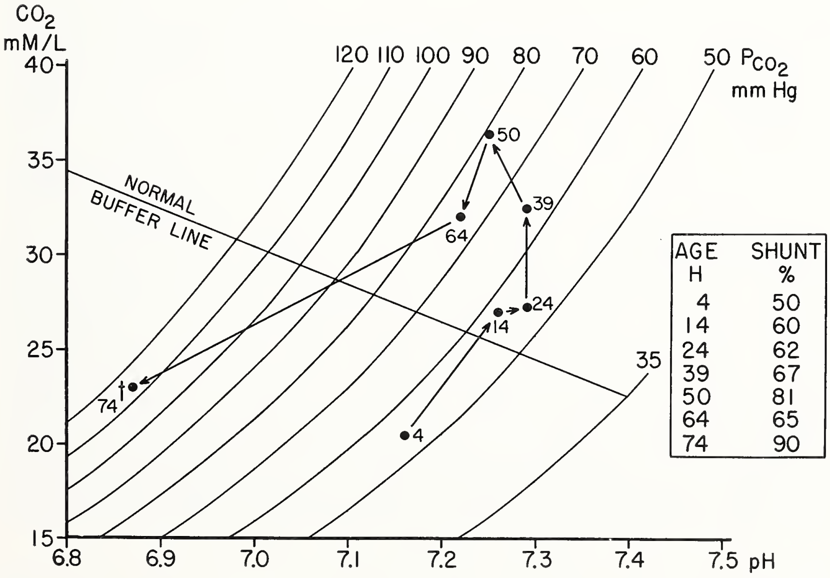

FIGURE 110.—Progressive changes of pH, pCO_2, CO_2 content, and percentage of right-to-left shunt in an infant with respiratory distress of Type I (see table 8).

when the infant died. At 4 hours, the pH, CO_2 content, and pCO_2 data indicated a moderate respiratory and metabolic acidosis, which, through treatment with alkali, was converted into the range of a metabolic alkalosis while the element of respiratory acidosis progressed. In our experience with this kind of treatment of severely sick infants, the anoxia has usually progressed even though the pH can be temporarily raised.

PATHOPHYSIOLOGICAL CORRELATIONS IN RESPIRATORY DISTRESS

Potter. I believe I can corroborate what you have been saying from pathologic material.

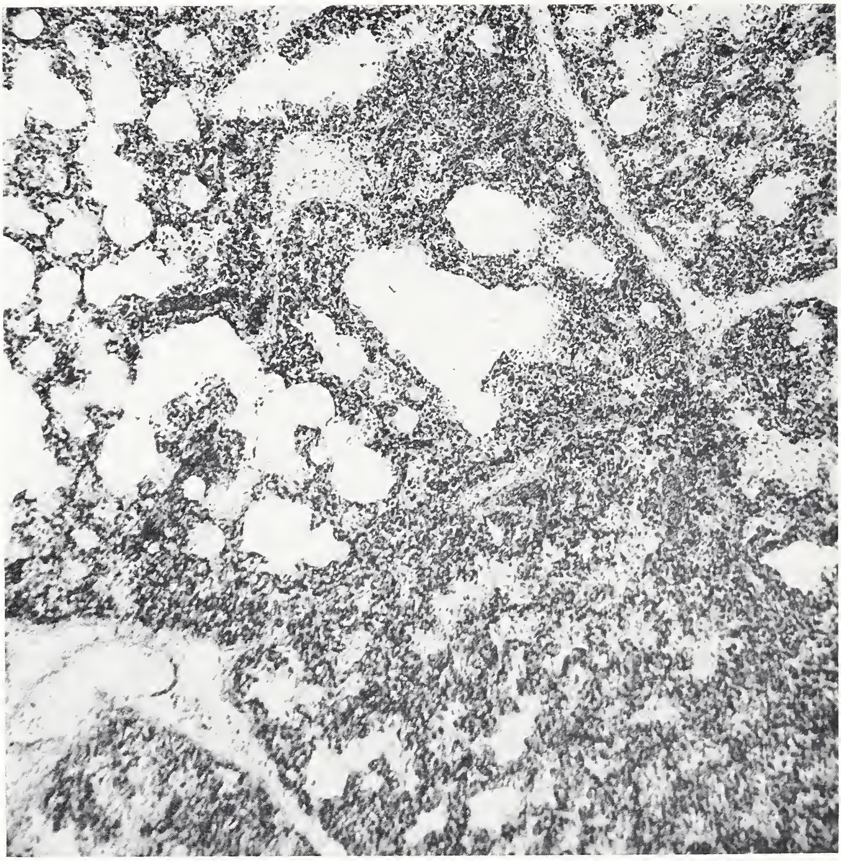

Figure 111.—Lung of infant surviving 12 hours showing irregular atelectasis. This is found as a terminal condition in most infants who die soon after birth from any cause even though lungs have previously been well expanded.

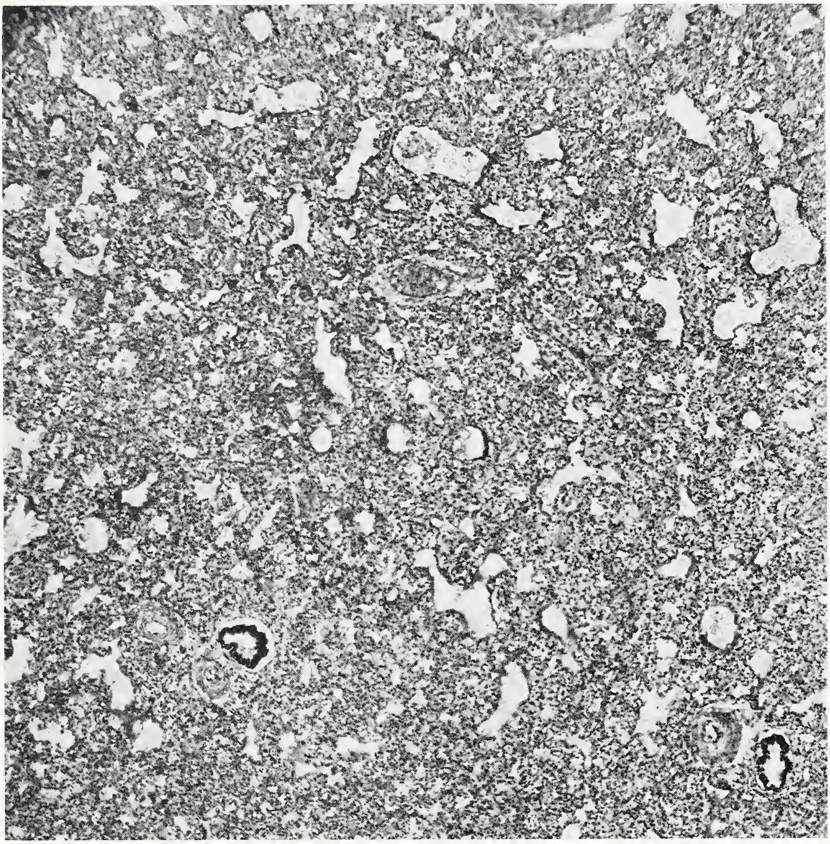

FIGURE 112.—Lung showing diffuse atelectasis with alveolar ducts lined by homogeneous material characteristic of hyaline-membrane disease. Reprinted, by permission, from Potter, E. L.: *Pathology of the Fetus and Infant,* ed 2. Chicago, Year Book Publishers, Inc. (Med), 1961.

Figure 111 shows the irregular air distribution seen in babies with respiratory distress who do not have hyaline membranes. There is a very irregular distribution of air. Large open spaces are distributed in otherwise atelectatic areas which explain the irregular X-ray shadows that Dr. Smith described in his Type II infants. In contrast, in typical hyaline-membrane disease (fig. 112) the tiny open spaces are lined by hyaline membrane and there is a massive, diffuse atelectasis which gives the "groundglass" appearance on X-ray and which is evidence that a large share of the blood is going through capillaries that have no contact with air spaces.

DAWES. Dr. Potter, these, presumably, were sections of lung that had been removed at autopsy with no distending pressure in them. If you would fix the same lung with some distending pressure within the air spaces, would there then also have been large areas of collapse?

Potter. I have a similar lung distended with fluid and these spaces all open up. There is a considerable difference in the appearance if the distension is with fluid or air. Following distension of a lung like this with air, the bronchioles and proximal alveolar ducts are hyperdistended, but no air gets into alveoli (fig. 113). Figure 114 shows another lobe of the same lung distended with formalin.

Comroe. Were the pressures the same in both?

Potter. I didn't measure them.

Comroe. May I make a plea to pathologists in general to treat the lung as an organ—and one that normally has a transpulmonary pressure—and a plea that they reestablish these pressures before fixing and sectioning the

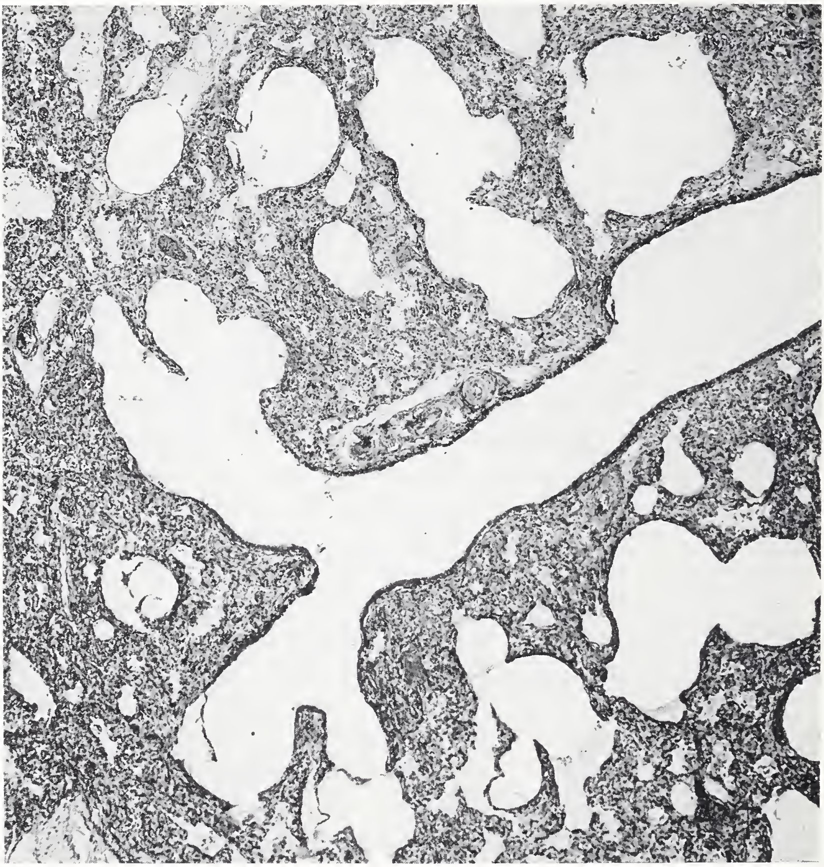

Figure 113.—Lung with hyaline membranes showing extreme hyperdistension of alveolar ducts resulting from attempt to inflate the lung with air. Reprinted, by permission, from Potter, E. L.: *Pathology of the Fetus and Infant,* ed 2. Chicago, Year Book Publishers, Inc. (Med), 1961.

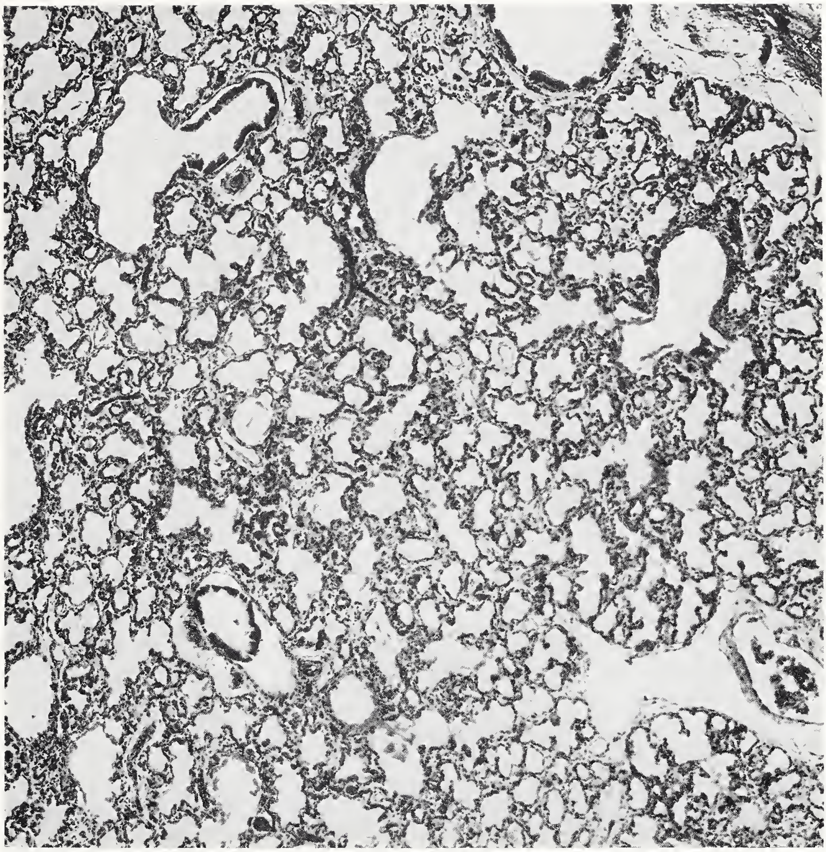

FIGURE 114.—Lung with hyaline membranes showing alveolar ducts and alveoli opened as a result of intratracheal introduction of fluid. Reprinted, by permission, from Potter, E. L.: *Pathology of the Fetus and Infant,* ed 2. Chicago, Year Book Publishers, Inc. (Med), 1961.

lung. In this way we would learn more than we ever could from sections of bits and pieces cut from here and there in a collapsed lung. This is something I have been crusading for, for years. You were the first pathologist that I know who ever distended the lung with *anything* before fixing and sectioning it. But it is important also to know what pressures are used, because one cannot make good (if any) physiopathologic correlation unless one knows what these are. I congratulate you on these pictures. I think it is wonderful to see the difference between fluid-distended and air-distended lungs.

CLEMENTS. We have data which bear on this aspect of the problem. An excised rat lung was inflated fully with air at room temperature and allowed to come down to a reasonably transpulmonary pressure, 6 cm of water. It remained in that state for 2 minutes, and then was instantaneously frozen.

Figure 115 shows the surface appearance of such a section, still frozen. One sees rather complete filling of air spaces and a uniform pattern of small air spaces. Figure 116 shows the effect of a comparable procedure, except that the excised lung was held at 47° C. Here, the gas is not at all in small air spaces. It is not filling alveoli; in fact, it is in the conducting airway and in alveolar ducts.

I think this merely shows that when one "melts" the surface of the lung, which is a procedure that *in vitro* prevents the development of low surface tension, or if it is low, raises it to 20 to 24 dynes per centimeter, one can pro-

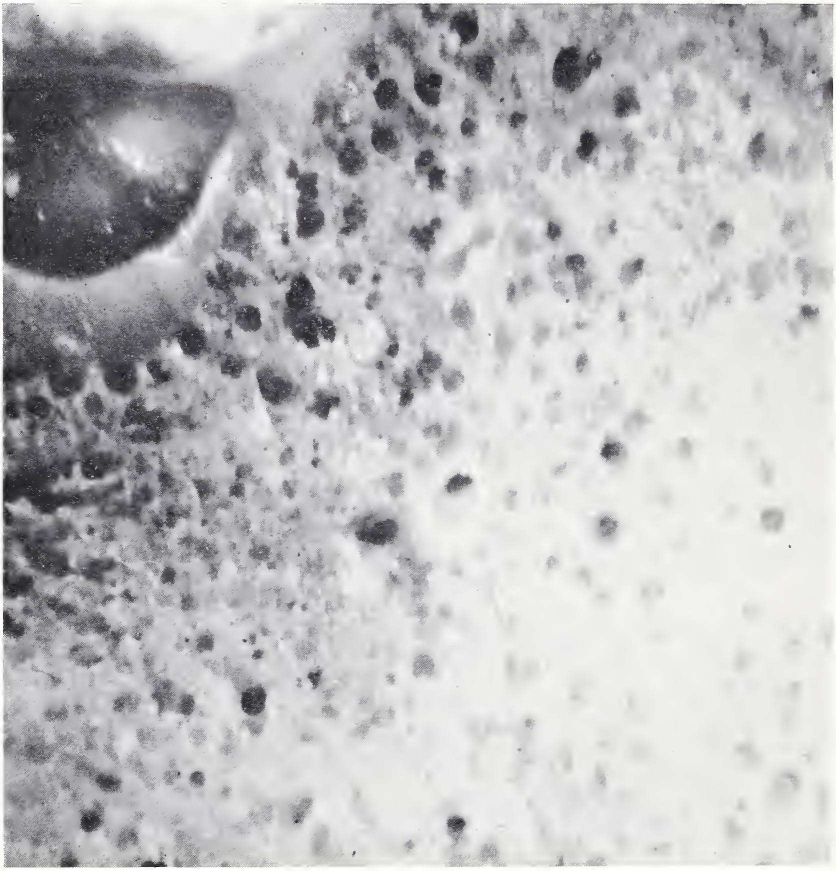

FIGURE 115.—Rat lung held at 24° C during inflation and deflation. After 2 minutes at 6 cm of water pressure rapidly frozen and sectioned while frozen (× 2). (Reproduced by courtesy of Dr. D. F. Tierney.)

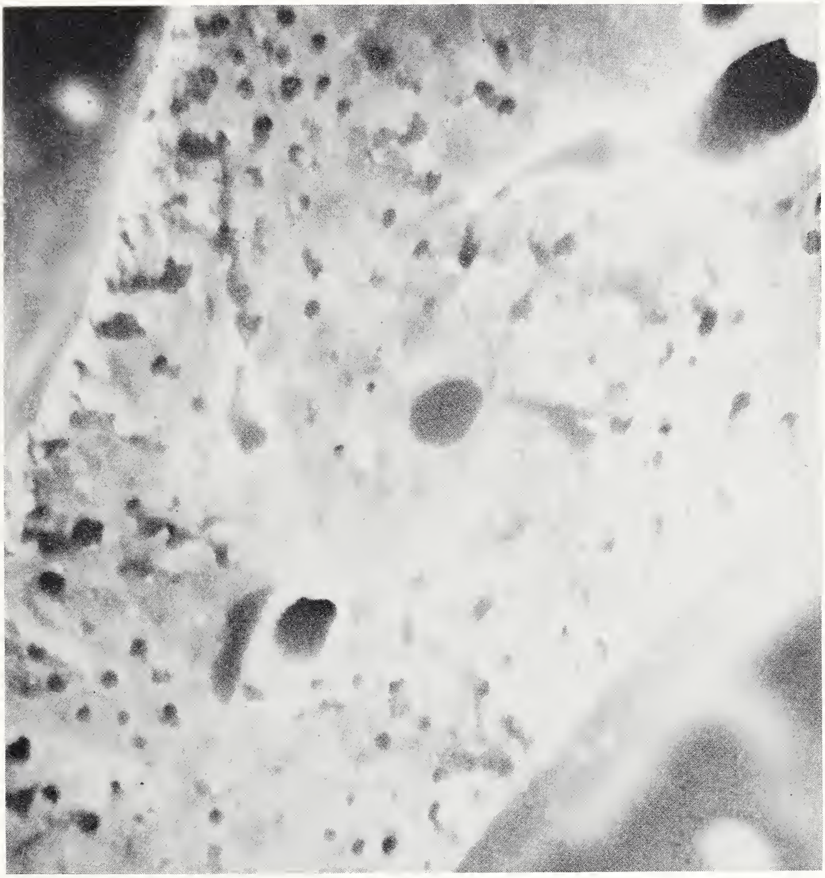

Figure 116.—Rat lung held at 47° C during inflation and deflation. After 2 minutes at 65 cm of water pressure rapidly frozen and sectioned while frozen (× 2). (Reproduced by courtesy of Dr. D. F. Tierney.)

duce, in the normal adult lung, a pattern of air distribution which is very similar to what is seen in Dr. Potter's pictures.

One more point. This is an entirely reversible phenomenon. If one cools the hot lung and studies it again at room temperature, it is just the same as it was before. This is also true of the measurements of surface tension.

Dawes. You mean you can shift the gas in and out of the alveoli by warming or cooling the lung?

Clements. Yes, if the pressure is held constant with an open system.

Avery. To reinforce what Dr. Potter has said—in fact, what we learned from the photomicrograph in her book—lungs with hyaline-membrane disease are distensible with saline. To answer Dr. Comroe's question to Dr. Potter—one can introduce more saline at much lower pressure (fig. 117).

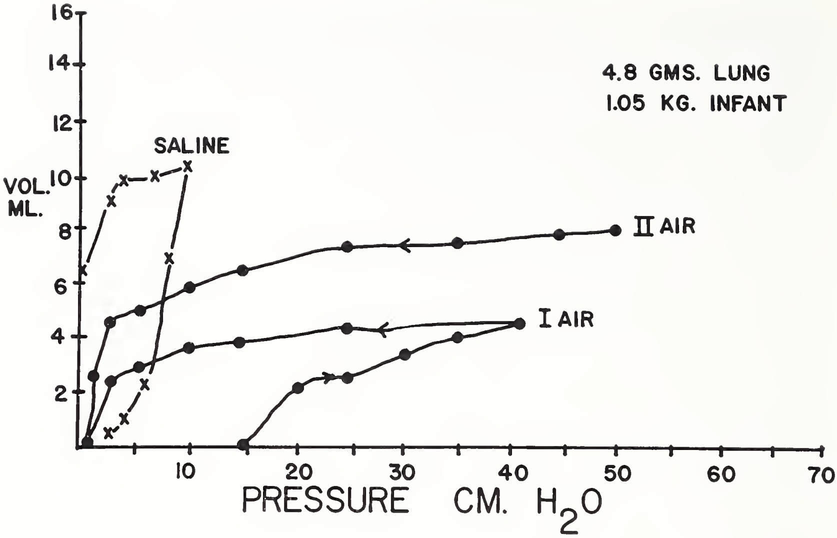

FIGURE 117.—Static pressure-volume curve of excised lung of an infant with atelectasis and hyaline membranes. Note that the lung is more distensible with saline than with air. The curve marked I AIR shows the amount of air in the lung after the first inflation. II AIR was after inflation to higher pressures and shows only the deflation limb. Reprinted, by permission, from Avery, M. E.: *The Lung and Its Disorders in the Newborn Infant.* Philadelphia, W. B. Saunders Company, 1964.

COMROE. Why, then, don't clinicians initially inflate lungs with saline and then replace it with air?

AVERY. Then what would the surface tension be?

CLEMENTS. When one does this with animals, the result is very unsatisfactory because of extensive destruction of alveolar cells and generation of pulmonary edema flow.

COMROE. Suppose we don't use saline, but use something which has surfactant in it for the first distension?

CLEMENTS. I would like to leave that as a question for the future.

BRUNS. Why not deliver the infant under saline until it expands its lungs with fluid?

POTTER. You don't have to do this experimentally. The fetus frequently does it for you *in utero*. He will always do it when he is asphyxiated.

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Circulatory Adjustments After Birth

RUDOLPH. It is relevant to discuss the hemodynamic arrangements of the fetal circulation before discussing some of the changes which occur during and after birth.

Because of the large communication at the ductal level in the fetal circulation, there is equalization of pressures between the pulmonary and systemic circulations. In view of this, the left and right ventricles behave as a common ejection chamber. Furthermore, since the communication between the two circulations is between the two great vessels, diastolic pressures are also equal beyond the semilunar valves. In such a system, the selective flow of blood is not determined by pressure relationships but by relative resistances in the different parts of the circulation. Resistance to blood flow through the placenta is relatively low and blood flow is high there, whereas, because vascular resistance is much higher in the lung, pulmonary blood flow is relatively low.

Immediately after birth, no major deviation in this particular arrangement of the circulation occurs, but changes in vascular resistances are predominant. With the elimination of the placental connection, a relatively low resistance circulation is removed, and the circulation arising from the aorta, that is, the infant's systemic circulation, now provides a very high resistance circuit.

The pulmonary circulation also undergoes rapid changes. A rapid decrease in pulmonary vascular resistance occurs—the absolute degree of which is somewhat indefinite at this time. This is associated with either mechanical expansion of the lung with air, or exposure of the vessels to higher oxygen levels, or both.

As long as the ductus remains wide open, blood flow to the systemic and pulmonary circulations will still be determined by their relative resistances. The situation is comparable to that seen in either the infant or older individual with a large communication between the two ventricles or between the aorta and pulmonary artery. If pulmonary vascular resistance is higher than systemic resistance, blood will flow preferentially into the systemic circulation, away from the lungs, whereas if pulmonary vascular resistance is lower than systemic, blood will obviously flow from the aorta into the pulmonary artery, and there will be an increase in pulmonary circulation.

DAWES. Are you assuming in this that the outputs of the two sides of the heart are exactly equal?

RUDOLPH. It doesn't really matter, if there is a large communication between the aorta and the pulmonary artery or between the two ventricles.

In the newborn infant, present evidence indicates that the ductus remains open for some time after birth. We have done a number of studies on mature, apparently normal, newly born infants. These suggest that the ductus may remain functionally patent for a period up to 10 to 15 hours after birth.[1] These studies have since been confirmed by further observations by ourselves, as well as by Moss, Emmanouilides, and Duffie.[2] The ductus is not always open for this period; in some infants it is functionally closed within an hour. This is not anatomic closure, since it is possible to pass a catheter through the ductus during the first day of life and still find no evidence of any physiologic shunt.

Within the first hour after birth, ductal shunting may be bidirectional. This can probably be explained on the basis of phasic variations of pressure between the aorta and pulmonary artery. As first noted by James,[3] the right-to-left shunt through the ductus usually disappears within the first hour. Left-to-right shunt, however, may be present for as long as 10 to 15 hours.

A word of caution should be given regarding the use of blood obtained from a catheter passed through the umbilical artery into the descending aorta in determining the alveolar-arterial gradients. One may not be measuring what one really wants to measure, namely, pulmonary venous pO_2 and pCO_2, if one collects blood from the descending aorta, particularly within the first hour in a normal infant, and even considerably later in a sick infant. Even left atrial blood may not be reliable during the first few hours after birth, since there frequently is also right-to-left shunting through the foramen ovale, particularly if the infant is distressed. Anything which may increase pulmonary vascular resistance, or any interference with ventilation, such as crying or a Valsalva maneuver, may create a right-to-left shunt through the foramen ovale. We have noted considerable differences in pulmonary venous and left atrial blood oxygen saturation and pO_2 in some infants.

COMROE. When does that difference stop?

RUDOLPH. I don't know. I can only say that it occurs for several days after birth.

As Dr. Dawes has mentioned, the pulmonary vasculature *in utero* is extremely sensitive and reactive to a number of influences. What happens after birth? Within the first 2 to 3 days, there is a marked reactivity of the pulmonary vessels. We have seen this in animals as well as in human infants. Hypoxia causes a marked vasoconstrictor response, and acetylcholine infusion, a definite vasodilator response. Administration of oxygen in some infants results in a considerable decrease in pulmonary vascular resistance, but there have been infants in whom there has probably been some hypoventilation.

When the healthy infant becomes 5 or 6 days old, the response of the pulmonary vessels to hypoxia or to acetylcholine decreases rapidly. In the newborn puppy the response to acetylcholine and hypoxia is lost within 6 to 7 days. This relates very clearly in some species, such as the puppy and the goat, to the time when the pulmonary vascular resistance approaches adult levels. The pulmonary arterial pressure drops very rapidly within the first day and, depending on the species, reaches adult levels or near adult levels within a matter of 6 to 14 days; in the puppy, it is within 6 days, in the goat it is about 14 days, and in the human, it seems to be about 10 days.

COMROE. Dr. Rudolph, how long does it take for a marked reduction to occur in the quantity of smooth muscles in the pulmonary arterioles?

RUDOLPH. This occurs very rapidly. It was first believed that the musculature in the pulmonary vessels took about 4 to 6 months to regress to the adult type, but these studies were based mainly on infants who had died with congenital heart disease. More recent studies have shown that the smooth muscle in the pulmonary arteriolar walls has largely disappeared within 2 to 3 weeks in the human infant; this fits very well with the physiological responses as well as with the pressure measurements.

We have studied in an animal model the effects of a left-to-right shunt through the ductus when pulmonary vascular resistance is reduced to normal. Such a shunt will result in an increase in pulmonary circulation with increased return of blood to the left ventricle. We have shown that the rapidity with which the left ventricle is presented with an increased volume load will, to a great extent, determine whether or not it will fail. For example, in the adult dog, in which a shunt is introduced between the aorta and pulmonary artery, sudden opening of the shunt will result in left ventricular failure due to the large volume presented to the left ventricle. If, on the other hand, this is done gradually over several minutes, the ventricle may be able to tolerate the load. The ability of the left ventricle to handle the load is also determined by the period allowed for left ventricular adaptation. Thus, if the shunt is widely opened within a day or two after its induction, failure may occur, but if it is opened slightly at first, then opening widely after a week may not produce failure. This suggests that the rapidity with which pulmonary vascular resistance drops may be quite important in determining the ability of the left ventricle to handle a load presented to it.

CIRCULATION IN INFANTS WITH RESPIRATORY DISTRESS

RUDOLPH. In a group of 10 infants with severe respiratory distress syndrome who were studied at Boston Lying-In Hospital at various times after birth, we found that during the time they had respiratory distress a large left-to-right ductal shunt was demonstrated.[1] In some, a right-to-left shunt was simultaneously observed. The left-to-right shunts were of considerable magnitude—much greater than any of the left-to-right shunts we observed in normal infants. In addition, some of these infants were well beyond the age of 10 to 15 hours, the time the ductus is usually closed in the mature infant.

JAMES. There has always been a question in my mind about the interpretation of these data. Were the infants receiving oxygen during the catheterization? If they were, did you measure the pO_2 as well as the oxygen saturation? This is important because if there was a high pO_2 in left atrial blood with the infant breathing 100 percent oxygen, there could be quite a large right-to-left shunt at the ductus level which would not be revealed by a drop in saturation but would be by a drop in pO_2.

RUDOLPH. None of the arterial blood oxygen saturations was above 92 percent. The infants were not receiving 100 percent oxygen, and the levels of oxygen saturation were never high enough that we were concerned with the problem of oxygen dissolved in plasma.

JAMES. Were these in the left atrium?

RUDOLPH. We had some left atrial samples, and they also showed no saturations above this level.

COOK. It is possible, however, that the oxygen you were administering did produce some vasodilatation of the pulmonary artery and increased an already existing shunt.

RUDOLPH. This is perfectly possible. We have recently done further studies in similarly affected infants in whom a catheter was passed retrograde through the umbilical artery. We have confirmed the earlier findings by means of cineangiographic studies. A large left-to-right shunt through the ductus in these infants was demonstrated when contrast medium was injected into the left atrium or ascending aorta.

STAHLMAN. We have approached both the transitional circulation and the circulatory adjustments in babies with respiratory distress syndrome somewhat differently. We ordinarily do not see distressed babies until they are several hours of age and at which time catheters* are put in the umbilical artery and umbilical vein. The venous catheter is threaded into the left atrium under electrographic and pressure control. Indicator dilution curves are made with injection into the left atrium, using a bolus, 0.2 ml usually, of indocyanine dye, with the pullout from the distal aorta. After we are satisfied with the curves, blood gases and pressures, the atrial catheter is withdrawn to the level of the diaphragm, then advanced about

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*Number 5 French plastic feeding tubes with side holes and with a platinum bead (for fluoroscopic identification) embedded in epoxy cement which fills the dead space.

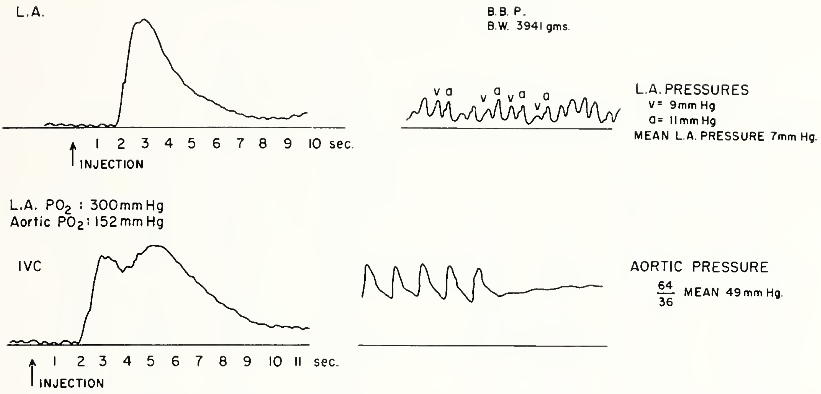

Figure 118.—Indicator dilution curves, aortic and left atrial pressures on a 3,941 gm baby in severe respiratory distress due to intrauterine aspiration pneumonia. The left atrial injection shows no left-to-right ductus shunt, while the inferior vena caval injection shows a very large right-to-left shunt. (See text for additional details.) Reprinted, by permission, from Stahlman, M. T.: Treatment of cardiovascular disorders of the newborn. *Pediat Clin N Amer 11: 363–400 (May) 1964.*

0.5 cm above the diaphragm, and another injection is made into the inferior vena cava.

The normal baby has right-to-left ductus shunting before birth and it is bidirectional shortly after birth. The probable explanation for the postnatal right-to-left shunt is that peak pulmonary arterial pressure seems to be reached before peak aortic pressure. This subsides rather promptly with normal breathing, but left-to-right shunting persists for a matter of hours and our observations agree with Dr. Rudolph's. In contrast to this, shunting across the foramen ovale continues for 48 to 72 hours and may persist even longer.

With this background on normal babies, I would like to show some data on infants with respiratory distress. The first example is a baby with aspiration pneumonia (the Type II baby Dr. Smith described*). I show this to shed further light on the question of whether the alveolar-arterial (A-a) oxygen gradient is on the basis of pulmonary exchange alone or if some of it might be on the basis of extrapulmonary shunting (fig. 118). In this infant, left atrial pO_2 was 300 mm Hg and there was little or no left-to-right shunting through the ductus with left atrial injection. With an inferior caval injection, there was an enormous right-to-left shunt through the foramen and presumably through the ductus as well, since the pO_2 in the distal aorta was 150 mm Hg lower than in the left atrium. This baby was breathing 100 percent oxygen. He had a left atrial mean pressure of 7 mm Hg with V waves of 9 mm Hg and A waves of 11 mm Hg. In this baby the right-to-left shunt at the ductus and atrial levels resulted in a large A-a gradient, in contrast to the experience described by Dr. Smith. The more important point is that extrapulmonary shunting may account for a great deal of the A-a gradient. We have also seen this direction and magnitude of shunting in the Type I babies.

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*See page 191.

This observation may be important in managing infants with respiratory distress because the oxygen tension which perfuses the retina is the same as left atrial pO_2, not that measured below the ductus.

SYSTEMIC BLOOD PRESSURE

Stahlman. We have observed that aortic blood pressure in healthy infants, as well as in those with respiratory distress syndrome of graded severity, increases with time after birth. This is also true as far as birth weight is concerned. Arterial pressure as well as pulse pressure increases as weight increases. Thus, one must take age and birth weight into consideration in the interpretation of blood pressure values in infants with respiratory distress.

Another interesting observation was the change in aortic pressure when moderately distressed babies were given 100 percent oxygen by mask, then room air, and then 100 percent oxygen again (fig. 119). Both mean and peak aortic pressures rose, sometimes as much as 15 mm Hg, when babies breathed 100 percent oxygen.

PULMONARY-SYSTEMIC SHUNTS IN INFANTS WITH RESPIRATORY DISTRESS SYNDROME

Stahlman. The indicator dilution method is a rough technique for calculating pulmonary-systemic flow ratios and reflects relative, not exact, amounts of blood flow. In infants with respiratory distress syndrome none had ratios less than 2:1, and many had ratios greater than 3:1 or 4:1.

The indicator dilution curve which is characteristic of babies with very large pulmonary-to-systemic flow ratios is shown in figure 120. Another variety of indicator dilution curve is shown in figure 121 in a baby with a small pulmonary-to-systemic flow ratio. This baby had a rather modest left-to-right shunt, but when one injected into the inferior cava or antecubital vein, a right-to-left shunt was present. There is a good bit of evidence to support the belief that if one gets right-to-left shunting following injection of dye into the superior cava in a newborn infant, there is a shunt at the ductus and not just at the foramen ovale.

There seems to be a fairly consistent sequence of events in severely ill babies. In the early stages, these babies have large right-to-left shunts,

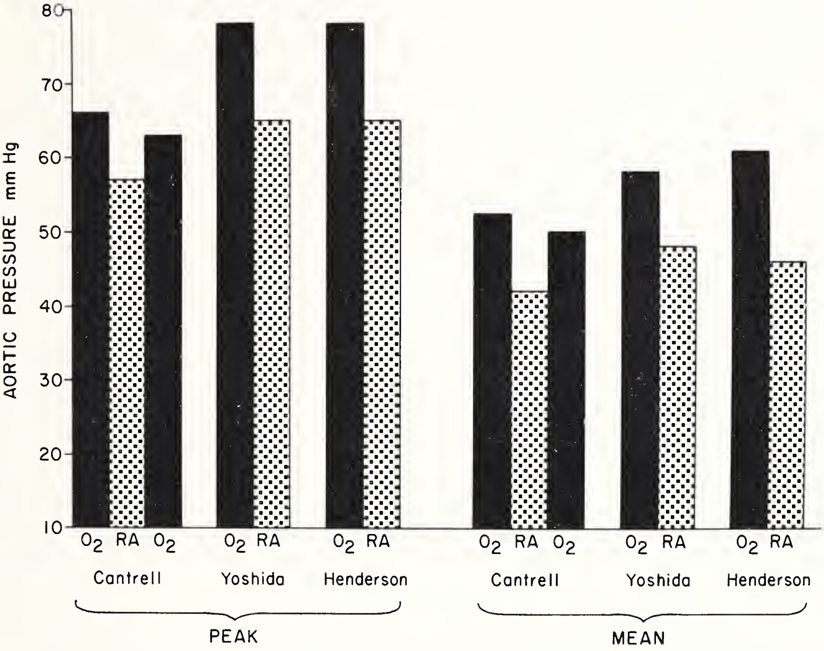

FIGURE 119.—The peak and mean aortic pressures are shown in three moderately ill babies with respiratory distress syndrome breathing 100 percent O_2 by mask and room air. Both peak and mean aortic pressures are significantly higher during high oxygen inhalation. Reprinted, by permission, from Stahlman, M. T.: Treatment of cardiovascular disorders of the newborn. *Pediat Clin N Amer 11: 363–400 (May) 1964.*

probably both at the ductus and foramen levels. As the baby gets older, the amount of right-to-left shunting becomes smaller, but the amount of left-to-right shunting becomes larger.

We have found that certain therapeutic manipulation may alter the shunting. Figures 122 and 123 show results in a baby who was extraordinarily ill on admission and who was put in an infant tank-type negative pressure respirator. The dye curves were made when the baby was 116 hours old, much improved, and was being weaned from the respirator. Left atrial injection curves with the respirator turned off showed a negligible left-to-right shunt. With the machine turned on, considerable increase in left-to-right shunting was apparent (fig. 122). One might conclude that there was an improvement when the respirator was turned off. However, inferior cava injection curves were also obtained (fig. 123). With the respirator off, the baby had a small left-to-right shunt but an enormous right-to-left shunt, which was abolished with the respirator on.

Thus, one may change the direction of shunts with negative pressure ventilation.

Dawes. I would like to give a warning about the use of indicator-dilution methods for measuring cardiac output in the newborn. In the only personal experience I have had (in newborn lambs), variations between the indicator-dilution and direct Fick methods were 25 to 50 percent.

Smith. Are there certain things which can be learned only by the dye dilution technique?

Rudolph. I would say that dye dilution curves are extremely helpful in sorting out where the level of right-to-left shunt is.

Stahlman. I disagree with Dr. Dawes. If one knows injection time accurately, if one maintains a constant withdrawal rate which is appropriate for the withdrawal system which one uses, if one knows where the injection catheter tip is, if one has a baby who is not crying, the dye dilution is a very good, very repeatable, and very harmless technique for demonstrating shunts in newborns, both in animals and in human beings, and can be quantitated in many instances. These are instantaneous injections and provide rapid measurements of flow instead of steady-state measure-

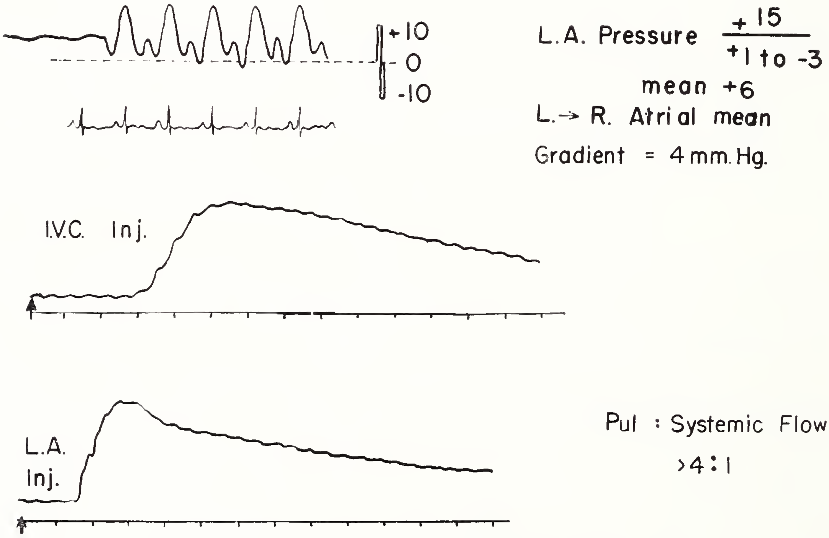

Figure 120.—Indicator dilution curves and left atrial pressure curve on a baby with respiratory distress syndrome with a large pulmonary-to-systemic flow ratio (>4:1). Both inferior vena caval and left atrial injection curves show a large left-to-right ductus shunt, and no right-to-left shunting is demonstrated. The left atrial pressure is elevated, especially the A wave, and there is a left-to-right atrial mean gradient of 4 mm Hg. Reprinted, by permission, from Stahlman, M. T.: Treatment of cardiovascular disorders of the newborn. *Pediat Clin N Amer 11: 363–400 (May) 1964.*

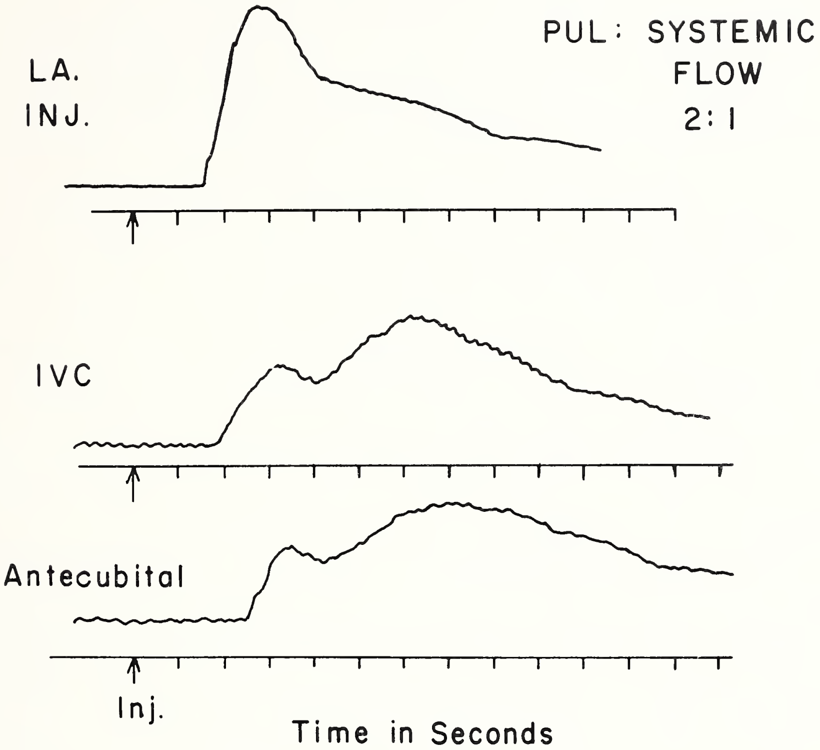

Figure 121.—Indicator dilution curves on a baby with respiratory distress syndrome with a small pulmonary-to-systemic flow ratio (2:1). All curves show a moderate-sized left-to-right shunt through the ductus arteriosus. Both inferior vena caval and antecubital injection curves show small right-to-left shunts, presumably, through both foramen ovale and ductus arteriosus. Reprinted, by permission, from Stahlman, M. T.: Treatment of cardiovascular disorders of the newborn. *Pediat Clin N Amer 11: 363–400 (May) 1964.*

ments which the Fick method relies on, so they are not measured over the same time period. Since one can give the blood back immediately if it is withdrawn into a siliconized sterilized syringe or sterilized catheter, the procedure can be repeated many times.

Klaus. What does the heart have to do with hyaline-membrane disease?

Comroe. Or conversely, what does hyaline-membrane disease have to do with the heart?

Rudolph. I think that obviously we get back to the problem which has been discussed previously, namely, that there are probably a number of different mechanisms responsible for respiratory distress. I do not know whether the disturbance of ventilation which occurs as a result of inability

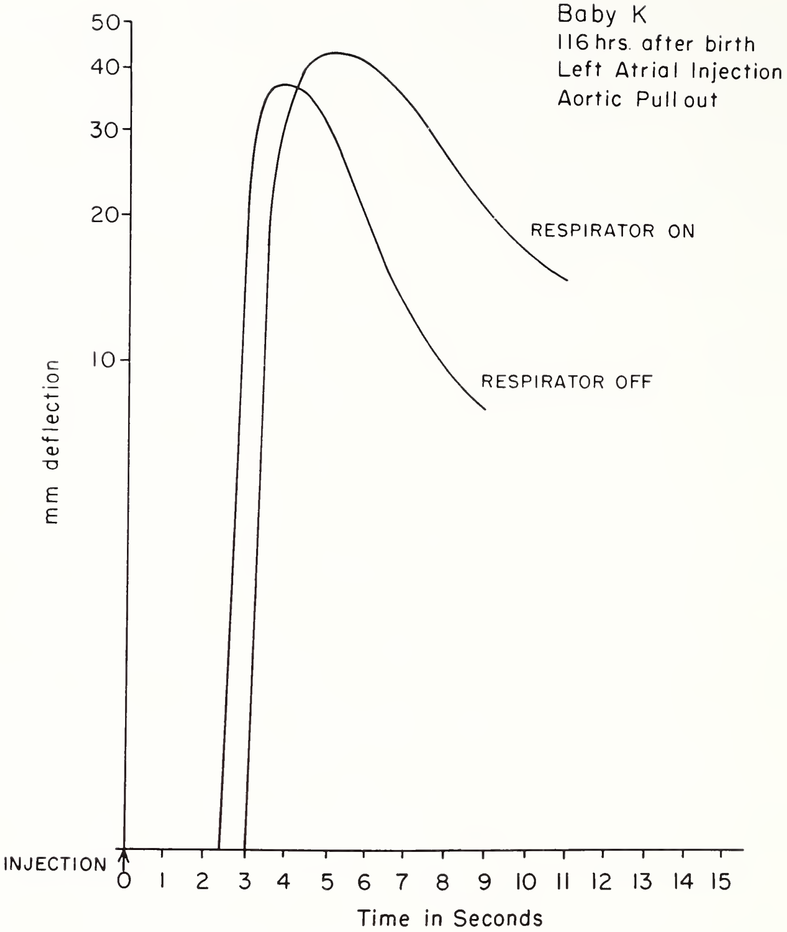

FIGURE 122.—Semilogarithmic plot of left atrial indicator dilution curves on a severely ill baby with the Monaghan respirator turned on and off. With the respirator off, no left-to-right shunt is shown, but a moderate-sized shunt is apparent with the respirator turned on. Reprinted, by permission, from Stahlman, M. T: Treatment of cardiovascular disorders of the newborn. *Pediat Clin N Amer 11: 363–400 (May) 1964.*

to expand the lungs produces a marked effect on the circulation. Indeed, we do have some information to indicate that the marked intrathoracic negative pressure which these babies develop is not responsible for the large ductal left-to-right shunt. In the experimental animal with an artificial ductus, increasing intrathoracic negative pressure by partially occluding the trachea does not produce an increase in shunt through the ductus.

I do not know whether the fact that many alveoli are not expanded has anything to do with flow through the lung circulation by altering pulmonary vascular resistance. As to the possibility of a cardiac problem affecting the lungs, the infant is different from the adult when left atrial pressure is increased and pulmonary edema develops. The adult with cardiac failure does not develop CO_2 retention until pulmonary edema becomes quite severe. In the infant, however, quite early in the development of failure, a

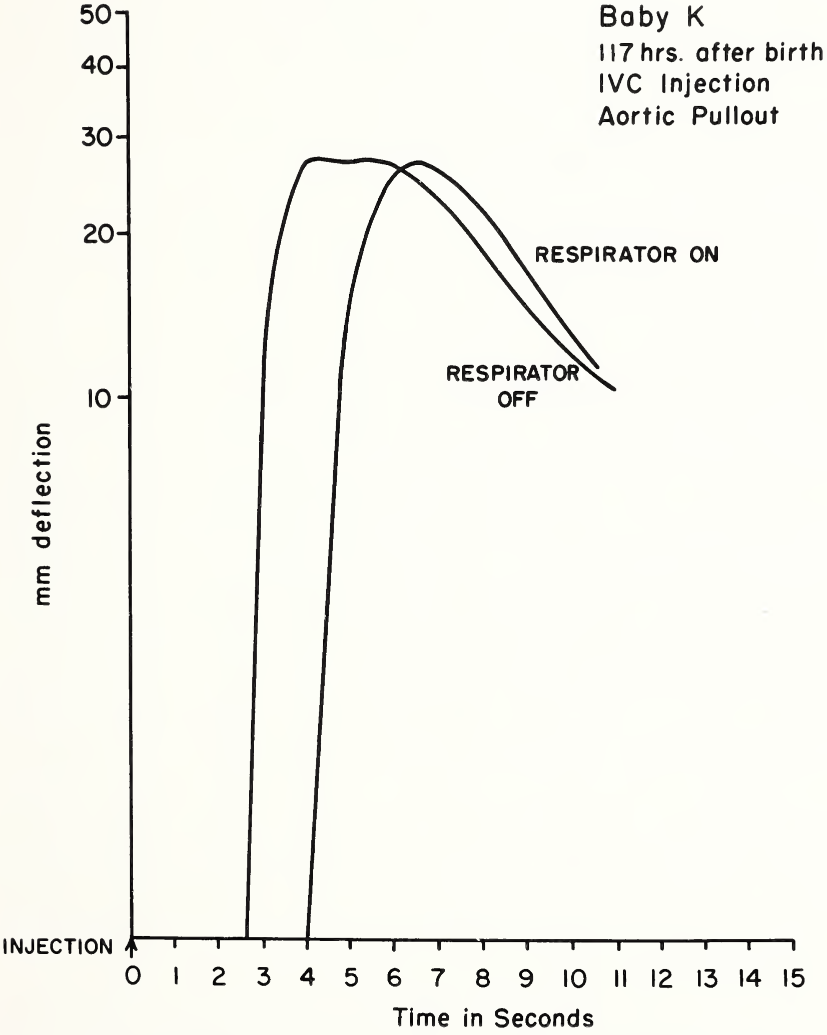

FIGURE 123.—Semilogarithmic plot of indicator dilution curves with inferior vena caval injection on the same baby as figure 120, with respirator turned off and on. There is a very large right-to-left shunt shown when the respirator is turned off which disappears when the respirator is turned on. Reprinted, by permission, from Stahlman, M. T.: Treatment of cardiovascular disorders of the newborn. *Pediat Clin N Amer 11: 363–400 (May) 1964.*

high arterial pCO_2 with respiratory acidosis and a lowered pO_2 may be observed.

In the older infant who has congenital heart disease with failure, we have observed that the left-to-right shunt persists in spite of an increase in pCO_2 and decrease of pO_2. Administration of high oxygen mixtures may lower pulmonary vascular resistance, thus further increasing left-to-right shunt.

I don't know whether there is an effect of this sort in the newly born infant. If pO_2 is low, this would tend to increase pulmonary vascular resistance. This may explain Dr. Stahlman's data—the increase in left-to-right shunt, which developed as the baby improved, could be due to an improvement in oxygenation and a consequent decrease in pulmonary vascular resistance.

In some infants with respiratory distress, I believe there is a definite cardiovascular disturbance. Even though it may not be the primary mechanism involved in the production of the disease, I do think it is important, because of the tremendous increase in flow to the left side of the heart, with an extra volume load on the left ventricle.

DAWES. What are the absolute values for cardiac output? There is evidence for a left-to-right shunt in these infants, but is left cardiac output increased, in absolute terms, over that in a normal infant or fetus? What about the energy supplies of the heart? If it is not getting enough oxygen, it is likely to go into failure. Have you evidence on these points?

STAHLMAN. We have been able to measure left ventricular output with indicator dilution curves in a few of these babies. In the presence of large left-to-right shunts, there is such rapid recirculation that it is not possible to obtain a slope which permits the calculation of cardiac output. When one has large right-to-left shunts and only small left-to-right shunts, however, one can calculate left ventricular output from curves obtained following injection into the left atrium. With little or no left-to-right shunt, the left ventricular output has been in the range of normal but it is increased two to three times in the presence of a moderate left-to-right shunt.

RUDOLPH. We have measurements of oxygen consumption in some of these infants which also indicate that the left ventricular output was high. But even if it were not greatly increased, a large left-to-right shunt might be of tremendous significance to an infant, since it would interfere with flow to the systemic circulation, and if diastolic pressure was low, coronary perfusion might be impaired.

PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS

RUDOLPH. There is evidence that the circulation in the premature infant behaves somewhat differently from that of the mature infant, mainly with regard to the rapidity with which changes occur in the ductus and pulmonary vessels. Some years ago, we did histologic studies on the ductus, pulmonary artery, aorta, and the umbilical vessels in the mature and premature puppy which indicated that the ductus has a very well-developed smooth muscle coat, which is not present in the adjacent pulmonary artery and the aorta. Furthermore, it was suggestive that the degree of muscle which was observed in the premature animal was considerably less than that in the mature animal.

More recently we have done some histochemical studies on the ductus, aorta, and pulmonary artery of the puppy to determine the amount of enzyme activity in these vessels. They revealed the presence of considerably less DPNase activity in the premature's ductal tissue than in the term puppy, which support the earlier observations.

As far as the pulmonary vessels are concerned, our studies, as well as those of Naeye,[4] have demonstrated the gradual development of a thick muscular coat in small pulmonary vessels of 50 to 200 μ size over the last trimester of pregnancy. Examination of the amount of muscle tissue relative to the size of the vessel in the human being shows that there is a rapid increase in the thickness of the muscular coat in these vessels from the seventh month of gestation. This muscle, of course, rapidly degenerates soon after birth.

The possibility that the pulmonary vessels in the premature infant do not have the same capacity to constrict, or that they may possibly undergo more rapid changes toward the normal adult type of vessel has been considered. We have found a high incidence of persistent patency of ductus arteriosus in the premature infant well beyond the first day of life.

STAHLMAN. How did you demonstrate it?

RUDOLPH. In some, only by the presence of a murmur, and in others by catheterization studies. The ductus may remain patent for several months, after which it may close spontaneously. The usual period has been 1 to 3 weeks after birth. Arterial saturation and pO_2 were normal in those infants in whom it was measured, so I do not believe the ductus was kept open by a hypoxemic stimulus.

KLAUS. Dr. Rudolph, what was the percentage of shunt through the ductus?

RUDOLPH. Most of the shunts were rather small, but we have seen infants with large shunts who actually did develop pulmonary edema in whom the ductus subsequently closed after digitalization. There was improvement of their failure and the ductus subsequently closed without surgical intervention.

The evidence for a different response of the pulmonary vasculature between mature and premature infants is indirect and derives from observations of infants with left ventricular failure secondary to a left-to-right shunt through a ventricular septal defect or patent ductus arteriosus.

In the mature infant, it is most unusual for left ventricular failure to develop before the second or third month after birth. In contrast, the premature infant may rapidly develop failure within the first month after birth.

This suggests that there is a more rapid decrease in pulmonary vascular resistance in the premature infant. Cardiac catheterization studies on these infants in failure reveal a low pulmonary vascular resistance with a large pulmonary blood flow.

Avery. Although this is more germane to what was said during the earlier discussion regarding the perfusion of the fetal lung, I want to relate why I am so interested in a report of a baby born in Lausanne, Switzerland, who died after 3 days of respiratory distress.[5] This infant weighed approximately 2.5 kilos. The autopsy was performed by Dr. Bozic. I consider his work in this case to be one of the important new bits of information on the pulmonary circulation and hyaline-membrane disease.

In all of the right lung and in the upper lobes on the left there was classic atelectasis and hyaline membranes. The left lower lobe was aerated and on section was, if anything, hyperinflated. There was no atelectasis and there were no membranes. Dr. Bozic then injected one color dye into the pulmonary artery and another into the aorta. He found that all that portion of the lung involved with atelectasis and hyaline membrane was perfused by the pulmonary artery. The portion of the lung which was aerated and normal received all its blood flow from aberrant vessels coming from the aorta.

Smith. Do you want to draw a conclusion?

Avery. Well, if one assumes that systemic pressures were higher than the pulmonary artery pressures and systemic flow was greater than the pulmonary artery flow, it would suggest that adequate perfusion of the lung is either protective or at least is associated with a normal lung. It points to the fact that we cannot ignore the relation of blood flow to the survival or function of the alveolar cells.

PERIPHERAL BLOOD FLOW

Karlberg. I would like to describe some recent work Dr. Olov Celander and coworkers carried out at the Children's Hospital in Göteborg. Some of this work is published,[6] some is not. They used the technique of venous occlusion plethysmography on the foot and calf of the newborn infant. All measurements were performed with the baby asleep in an incubator. The water in the plethysmograph was thermostatically maintained at a constant temperature.

With this technique it is possible to obtain hemodynamic data such as flow rates, pressure, and resistance on the peripheral systemic circulation. The maximal flow capacity at reactive hyperemia tells us about the vascularity of this tissue and the capillary filtration coefficient about capillarization.

A large number of full-term and premature infants with both normal and abnormal adaptation to extrauterine life have been studied. These data have been compared with what is known to apply for the adult. Important differences were found. The premature infant has a large resting blood flow, a relatively low arterial blood pressure, and a very low resistance to blood flow. The maximal blood flow capacity is high and the capillary filtration coefficient some six to seven times higher than that of the adult. A low blood flow, a higher pressure, and therefore a much higher resistance, characterize the hemodynamic situation in the adult. Maximal flow capacity is also considerably lower, as is the capillary filtration coefficient. Between these two extremes stands the normal full-term infant.

None of these functions of peripheral circulation is fixed; they vary with the conditions of the infant. The hemodynamic control of "resistance vessels" is mainly controlled by the sympathetic nervous sytsem. On the other hand, the number of capillaries open to circulation is largely regulated by local chemical influences. It is important to emphasize these differences: regulation of volume flow to a tissue is one consideration; the distribution of flow to capillaries is quite another.

After a normal delivery, the newborn infant has an increased sympathetic tone during the first hours of life, although a steady-state is reached by 12 hours in most infants (fig. 124). After a pathological delivery, particularly if asphyxia has occurred, the restrictive sympathetic influence on the rate of blood flow is far more pronounced and continues for a much longer time (fig. 125). It is obvious that dramatic hemodynamic alterations may occur despite a relatively normal blood pressure level. At the start of recovery from asphyxia, limb blood flow is reduced almost to nil and the resistance to blood flow is extremely high (160 PRU).

If a newborn infant is exposed to a low environmental temperature, the blood flow is decreased (fig. 126). At the same time, the capillary filtration coefficient may increase considerably. This inverse relationship between rate of blood flow and capillary surface area available to circulation appears to be a general compensatory mechanism. This has been shown to operate in the cat upon stimulation of sympathetic nerves. By this mechanism a reduction of blood flow (which may be essential to maintain hemodynamic stability) is counteracted by a more thorough distribution of blood.[7] The normally high capillary filtration coefficient in premature and full-term newborn infants, and its further tendency to increase at low ambient temperature, increases the likelihood for fluid filtration from the larger capillary surface area. This may explain why a cold infant often becomes edematous.

Some preliminary observations on premature infants with the idiopathic respiratory distress syndrome indicate that the "microcirculation" is very markedly altered. These babies have a more restricted blood flow and a higher resistance than do healthy prematures. However, the most important

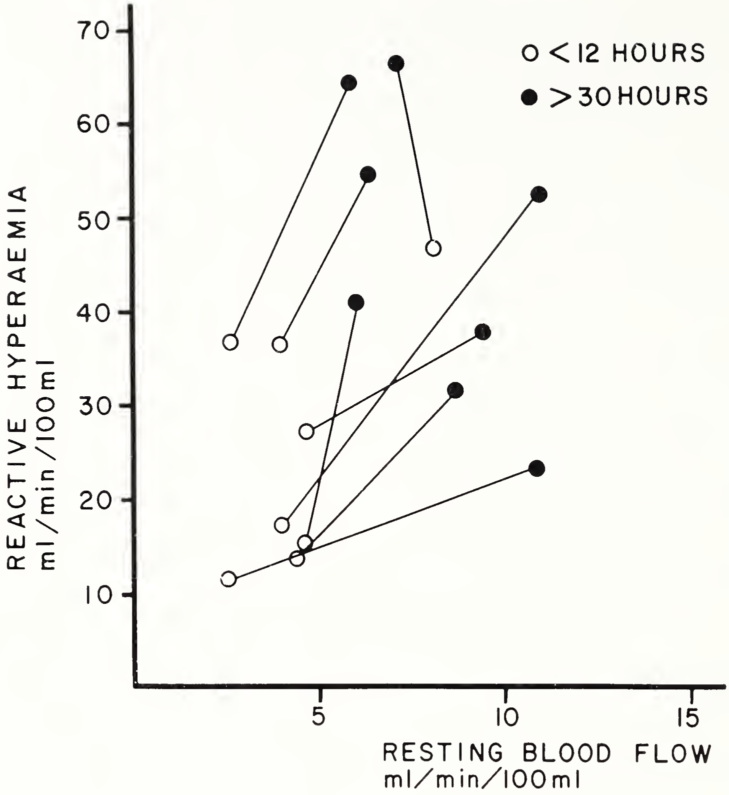

FIGURE 124.—Resting blood flows and reactive hyperaemia peak flows at 40° C. in early and late neonatal age. Note the increases of blood flow capacity during the first few days of life. Reprinted, by permission, from Celander, O., and Mårild, K.: Reactive hyperaemia in the foot and calf of the newborn infant. *Acta Paediat (Stockholm) 51: 544–552 (Sept) 1962.*

feature of the peripheral circulation appears to be the very high capillary filtration coefficient. Figure 127 shows serial measurements of capillary filtration coefficients in a pair of nonidentical twins, only one of whom had the respiratory distress syndrome. It is tempting to speculate on what would happen in the pulmonary circulation if similar changes in microcirculation also occurred there. It could explain why interstitial edema is usually an early and prominent part of the pulmonary pathology in the idiopathic respiratory distress syndrome.

SEGAL. We have similar data on blood flow measured in the hand using a temperature-controlled air system. Although we have no studies on filtration, the observations on blood flow are similar; furthermore pulse volume is also reduced when respiratory distress is severe.[8]*

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*Investigation supported by National Health Grants (Canada) 609–13–15.

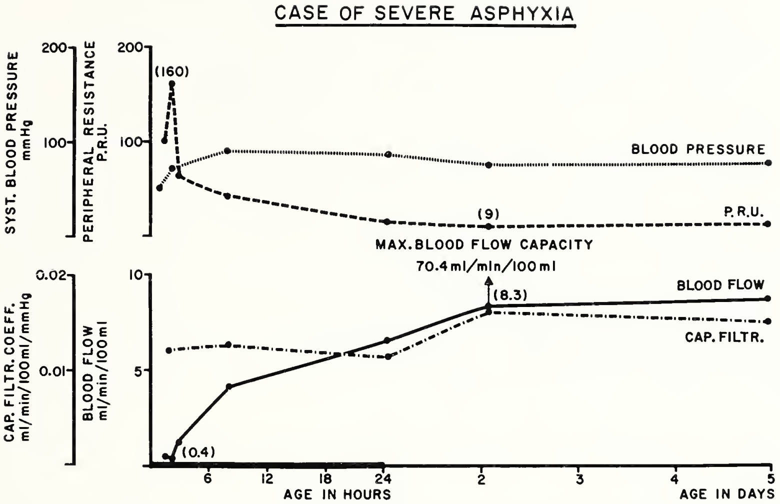

Figure 125.—Changes in blood pressure, blood flow, resistance to flow and capillary filtration coefficient (CFC) in the foot and calf of a newborn infant recovering from severe extrauterine asphyxia. Note the relatively small changes in systolic blood pressure but how behind this "silent surface" dramatic changes take place in the control of the vascular bed of the extremity. Note the extensive range of local blood flow which at maximal vasodilatation is around 70 ml/min/100 ml. Normally, only some 10 percent of this capacity is "taken out" as resting blood flow. During asphyxiation, blood flow is almost nil. (Reproduced by courtesy of Celander, O., and Berg, K., personal communication.)

EXPERIMENTAL RESPIRATORY DISTRESS SYNDROME

Caldeyro-Barcia. Does the respiratory distress start during intrauterine or extrauterine life?

Stahlman. Intrauterine, I think. We can produce it in intrauterine lambs but cannot produce it with the same or multiple techniques in extrauterine lambs.

Oliver. But, surely, it can occur as a result of early extrauterine events.

Stahlman. It may be related to intrapartum events, but I doubt very much if this syndrome can develop in a baby once he has established regular breathing.

Villee. How is the respiratory distress syndrome produced intrauterinely in lambs?

Stahlman. Prior to term, ewes are given 200 mg of promazine hydrochloride (Sparine) which makes the ewe hypotensive. Twenty-four hours later we deliver the lamb by cesarean section.

Comroe. What is your percentage of success?

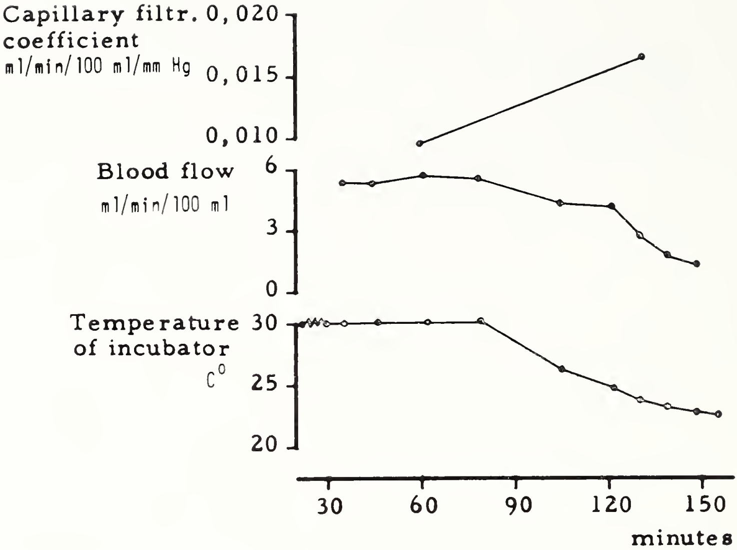

Figure 126.—Changes of blood flow and capillary filtration coefficient (CFC) in a newborn child when exposed to a lowered ambient temperature. Note the increase of CFC while blood flow was reduced. Reprinted, by permission, from Celander, O., and Mårild, K.: Regional circulation and capillary filtration in relation to capillary exchange in the foot and calf of the newborn infant. *Acta Paediat (Stockholm) 51: 358–400 (July) 1962.*

Stahlman. We have delivered 44 lambs by cesarean section between 110 and 146 days. Twelve of them had mild respiratory distress, 4 had moderate respiratory distress, and 28 had severe respiratory distress. Of those with severe respiratory distress, 24 demonstrated some degree of hyaline-membrane formation at autopsy.

Levine. Can you produce the same picture if you deliver the lambs prematurely by cesarean section without the drug?

Stahlman. We haven't done that. However, there is no question but what the degree of immaturity has something to do with it. The more immature the lamb, the more likely will severe respiratory distress develop and hyaline membranes be found at autopsy.

Arterial pH was followed on these lambs. It was lower in the sickest lambs and more normal in mild and spontaneously delivered lambs throughout the course of their disease. Arterial pCO_2 was also followed serially, and the degree of CO_2 retention correlated well with the degree of respiratory difficulty. Arterial pressures were not significantly different with differing grades of severity. The picture was more or less the same as that seen in human infants. Similarly, the blood lactic acid levels on the lambs corresponded with lactic acid levels in human infants and were considerably higher in severely ill lambs than they were in normal or mildly ill lambs. Indicator dilution curves were quite comparable to those found in human infants.

The pathologic findings in these lambs seem to be a function of the duration of survival. In an animal which has died within 10 minutes after birth the small pulmonary arterioles are tremendously constricted. There is edema of the adventitia and swelling of the nuclei of the smooth muscle layer.

Shortly after, the lamb with constricted small arterioles may show a beginning slough of epithelial cells into the lumen of alveolar ducts and respiratory bronchioles. In the next stage, one sees almost completely occluded arterioles immediately adjacent to either alveolar ducts or respiratory bronchioles and the beginning appearance of edema fluid with vacuolization of the

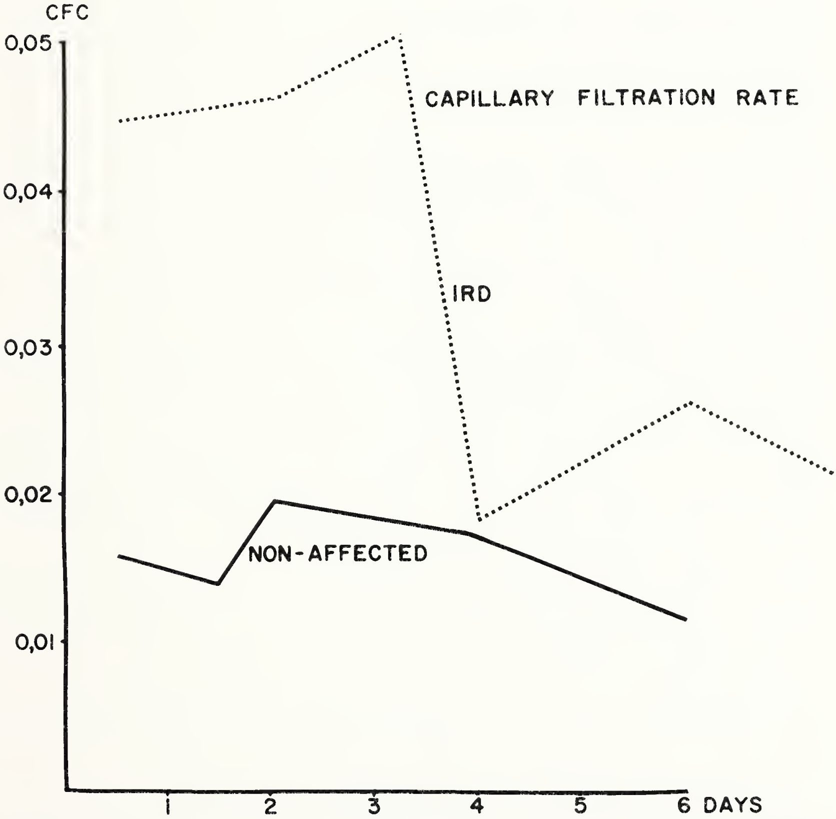

FIGURE 127.—Repeated measurements of capillary filtration coefficient (CFC) during the course of an idiopathic respiratory distress syndrome in one twin, whereas the other (nonidentical) remained unaffected. (Reproduced by courtesy of Celander, O., and Berg, K., personal communication.)

lining epithelial cells. Next, the epithelium of the alveolar ducts and respiratory bronchioles completely sloughs except for remnants here and there, and it becomes a mass of cells with pyknotic nuclei. Edema fluid may fill the lumen.

At autopsy of a lamb which has survived more than 5 hours, one sees an unconstricted ductus arteriosus, a dilated right atrium, dilated superior and inferior cavae, an engorged liver, and dark purple liverlike lungs. In addition, pulmonary edema, a mass of cell debris, and the protein-containing fluid in the alveolar ducts can be seen. This material begins to look like hyaline membranes, and at this stage one sees capillary engorgement and much less air in alveoli. By 6 to 7 hours, well developed hyaline membranes are present, with loss of identification of cell components, capillary dilatation, and widespread atelectasis.

Dawes. Earlier, Dr. Rudolph suggested that there might be many causes of respiratory distress in the newborn. Is there really any evidence that this is a disease of multiple causes, or is it just a result of a sufficient degree of asphyxia, either before or shortly after birth?

The same clinical picture and biochemical changes, as were produced by Dr. Stahlman's procedure, can be produced in lambs delivered by cesarean section under local anesthesia, together with 10 to 12 minutes asphyxia. This is true as well in the monkey. There is probably a common element in these phenomena.

Comroe. Do you believe that the common factor is systemic asphyxia or ischemia of lung tissue?

Dawes. I suspect pulmonary hypoxia is the common element caused by asphyxia of the fetus. The same is true of Dr. Cook's work, isn't it?

Cook. We have tried to asphyxiate fetal lambs, and our relatively few data support the data of Dr. Stahlman. We have given controlled asphyxia to fetal animals and then tried to resuscitate and examine them clinically, biochemically, and pathologically. We have found that the mature fetal lamb has a remarkable resistance to asphyxia.

Dawes. How did you produce asphyxia?

Cook. We hypoventilated the ewes. In some cases we used 14 to 16 percent oxygen in addition to hypoventilation.

Caldeyro-Barcia. How long did you asphyxiate the mothers?

Cook. The pregnant ewes were asphyxiated for between 2 and 3 hours. We could not produce severe asphyxia immediately. PaO_2 finally reached 10 to 14 mm Hg in the fetus and $PaCO_2$, 80 to 100 mm Hg.

The important point is that the animals which developed respiratory distress with loss of surfactant were premature although they were of an age when they could have been expected to have surfactant present. We still have to separate the factors leading to the respiratory distress, that is, the effect of prematurity *per se* versus asphyxia. We hope that the newborn lamb may provide an experimental model that will be useful for examining mechanisms of this disease and for evaluating therapy. It appears to us that it is crucial to study the premature animal.

Dawes. I am sure you will get a much higher incidence in the premature animal. Perhaps Dr. Comroe should mention the experimental production of hyaline-membrane disease in adult dogs.

Comroe. These experiments were performed by Drs. Clements, William Tooley, and others. The pulmonary artery was either ligated or, in some cases, the blood flow through it was occluded for several days by an internally placed balloon which was distended so there was no interference with nerves to the lung.

Dawes. This is a very useful lead. An experiment on similar lines could be carried out by causing pulmonary ischemia in one lobe or lung of fetal lambs and examining the results at different stages of maturity.

Comroe. What is the metabolic rate of the fetal lung? If it is high, and if the pulmonary arterioles are exquisitely sensitive to stimuli, such as low pO_2 or high pCO_2, their constriction could lead to a decreased supply of metabolites and cell death.

Villee. The fetal lung has a fairly high rate of oxygen consumption and of metabolism in general. It accumulates glycogen, it secretes glucose, and its rate of oxygen consumption is about equal to that of the fetal liver.

Dawes. That is on the basis of tissue slices, isn't it?

Villee. Yes, these are inferences drawn from experiments with tissue slices. This is about the only way to make such measurements. It does seem clear that the fetal lung is not simply waiting quietly in the fetus for the first breath to occur, but rather, it has a number of functions during fetal life. Popják[9] has measured lipid metabolism in the fetal lung and finds that it occurs at a very respectable rate.

Ramsey. Embryos not only develop, they also live.

Segal. We are looking for a common factor for the development of respiratory distress syndrome in man or animal. Would the surface-tension scientists tell us whether the postperfusion syndrome is comparable to this syndrome, and if it is, whether studies have yielded a common factor which may be more precise than any we have been discussing?

PATHOGENESIS OF RESPIRATORY DISTRESS SYNDROME: UNIFYING CONCEPTS

Clements. On the basis of experimental evidence there are several conditions in which respiratory distress has been observed with four findings in common: (1) atelectasis; (2) the formation of hyaline membranes within the alveolar spaces; (3) overt or incipient cellular decay in the alveolar membrane; and (4) failure to demonstrate surface-active material when extracts are prepared.

The first of these conditions is idiopathic respiratory distress in the newly born and the similar state produced in experimental animals by Drs. Dawes, Cook, Stahlman, and their coworkers. It has also been noticed in association with respiratory distress after cardiopulmonary bypass and extracorporeal circulation, in psittacine and rheumatic pneumonitis. It occurs following and accompanying prolonged administration of 15 percent carbon dioxide. It has also been observed in rabbits after 3 to 4 days of administration of 100 percent oxygen at one atmosphere. In addition, it has been observed following the intravenous administration of furfural acetone, following unilateral pulmonary arterial occlusion on the affected side, following bronchus ligation on one side, following vagotomy in the guinea pig, and at least some features have been described in connection with prolonged systemic hypotension.

I would like to suggest a sequence of events which may explain how these diverse conditions are related (fig. 128). With reasonable intrapleural pressure swings, one cannot assure continuing ventilation and gas exchange unless there is a reasonable level of compliance. This implies expansion of the lungs, stability of the alveolar structure, and reasonable elastic characteristics of the individual air spaces.

If the ventilation is not maintained at a sufficient level, then perfusion of the alveolar regions cannot be maintained. If this happens, the metabolism of the cells making up the alveolar region cannot be sufficiently maintained, and those synthetic activities which depend upon the maintenance of oxidative metabolism will suffer. These would include interference with cellular barriers, transport functions, and secretory processes. This, in turn, would lead to failure of replacement of the alveolar lining material (sur-

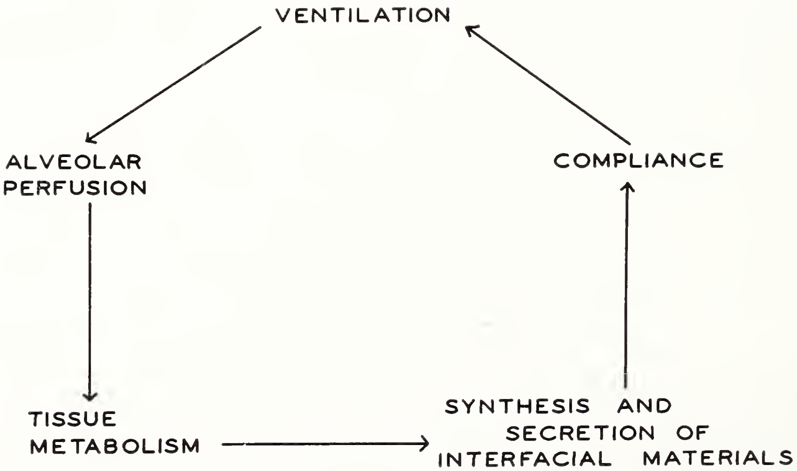

Figure 128.—Diagram illustrating interdependence of the cellular and transport functions of pulmonary alveolar tissue.

factant), leading to reduction in pulmonary compliance, thus completing the vicious circle.

This diagram illustrates two things to me. First, there must be interdependence of these phenomena, and second, the status of the alveolar cells, especially those epithelial cells that seem to have special secretory functions, plays a central role.

I would make the hypothesis that in these 12 natural or experimental disease states, and probably in some others, the primary insult to the lungs is diminution of pulmonary perfusion. It is obviously so in the case of pulmonary arterial occlusion. In respiratory distress, we can call on the reflex described by Dr. Dawes and his colleagues, that of the centralizing of the circulation, which in this instance may mean exclusion of the lungs, to some extent, from perfusion. In viral and rheumatic pneumonitis, pulmonary arteriolar inflammation and narrowing or occlusion of arteriolar lumina have been observed microscopically.

The acidosis resulting from long administration of 15 percent carbon dioxide and prolonged inhalation of oxygen at one atmosphere in some species probably also acts through pulmonary vasoconstriction or stasis.

Furfural acetone causes agglutination of red blood cells and might produce microembolism in the capillaries or small arterioles of the lung, which is the first organ to collect the emboli. It is reasonable to think that this same kind of phenomenon occurs in respiratory distress following extracorporeal circulation, where sludging of blood is observed in the vessels of the retina, for example.

A day or so following bronchus ligation, the pulmonary perfusion has also been shown to drop to a low level. It is a reasonable possibility that this happens following vagotomy of the guinea pig. Pulmonary vasoconstriction and hypoperfusion may also be operative in the "irreversible shock" which, according to Moon,[10] is sometimes associated with atelectasis and hyaline-membrane formation.

DAWES. How does prematurity fit into this? Is the incidence of this condition greater in the premature infant? Is the death rate greater?

COMROE. I would like to find out if the pulmonary arterioles are usually sensitive to low oxygen and high CO_2 tensions. They certainly are at birth and for a few days after birth. Then they seem to lose it.

CLEMENTS. There would be a wealth of reasons. Dr. Dawes has said that pulmonary vasoconstriction is more active earlier in fetal life. It may be that the metabolism of the alveolar tissues is at a higher level, and disproportion between demand and supply may occur more readily in the earlier state. The stores of crucial substances, such as phosphatides, in the alveolar tissues may also be smaller. Finally, we don't actually know the things which bring about premature delivery.

KLAUS. In the very immature infants, the alveolar lining cells may not have completely developed.

Cook. In answer to Dr. Comroe's question about prematurity, it seems probable that the number of inclusion bodies and surfactant may gradually increase. There may then be a critical period when there is just enough surfactant. At this point, however, a minimal insult or a minimal amount of inhibitor could produce disease, whereas it might be much more difficult to produce the same result in a more mature organism.

Avery. I would like to throw a little different light on this—nothing inconsistent with Dr. Clement's wheel of fortune—but merely to permit us in some situations to break into this at another level.

In three species there have been studies on the time of appearance of the detectable surface-active material from lung extracts. The mouse has only a 19-day gestation, but on the 18th day of that 19-day gestation, suddenly, surfactant can be detected. This is a very abrupt time of onset.

The lamb has little or no surfactant at less than 120 days, and it gradually appears between 120 and 130 days of a 147-day gestation. The human population is different in that some infants of low birth weight have relatively immature lungs. The time of appearance of surfactant is not at a given day but over a span of time in the 266-day gestation. So, on the basis of immaturity alone, there is a population at risk of being born with an inferior alveolar lining layer.

I don't want to imply that this can account for all the babies we see with hyaline-membrane disease. I do believe, however, that it accounts for the bulk of them, since most of them, if one includes atelectasis as well as atelectasis with membranes, are under 1,500 gm birth weight.

Comroe. Can these lungs be distended by fluid—the lungs that have no surfactant?

Avery. Yes, they can.

Cook. I have understood that most infants with respiratory distress do not show evidence of asphyxia at birth. I believe that there are some data from Dr. Smith's group which suggested that the babies of diabetic mothers who developed respiratory distress showed no evidence of asphyxia at birth.

James. I cannot agree that the majority of these babies are not asphyxiated at birth. Perhaps they are not as asphyxiated as the monkeys or the lambs. It would be interesting to know how asphyxiated Dr. Stahlman's lambs become during the period of maternal hypotension.

Figure 129 shows 94 infants who died at Babies' Hospital and in whom hyaline-membrane disease was confirmed at autopsy. By the Apgar score, three of these infants scored zero, 19 scored 1, 17 scored 2, and 6 scored 3; thus, nearly 50 percent of the babies scored 3 or less at 1 minute of age. Only a small proportion were in the so-called vigorous group, scoring 7 to 10.[11]

Smith. The study Dr. Comroe referred to indicated that many infants who developed respiratory distress did not show evidences of asphyxia in

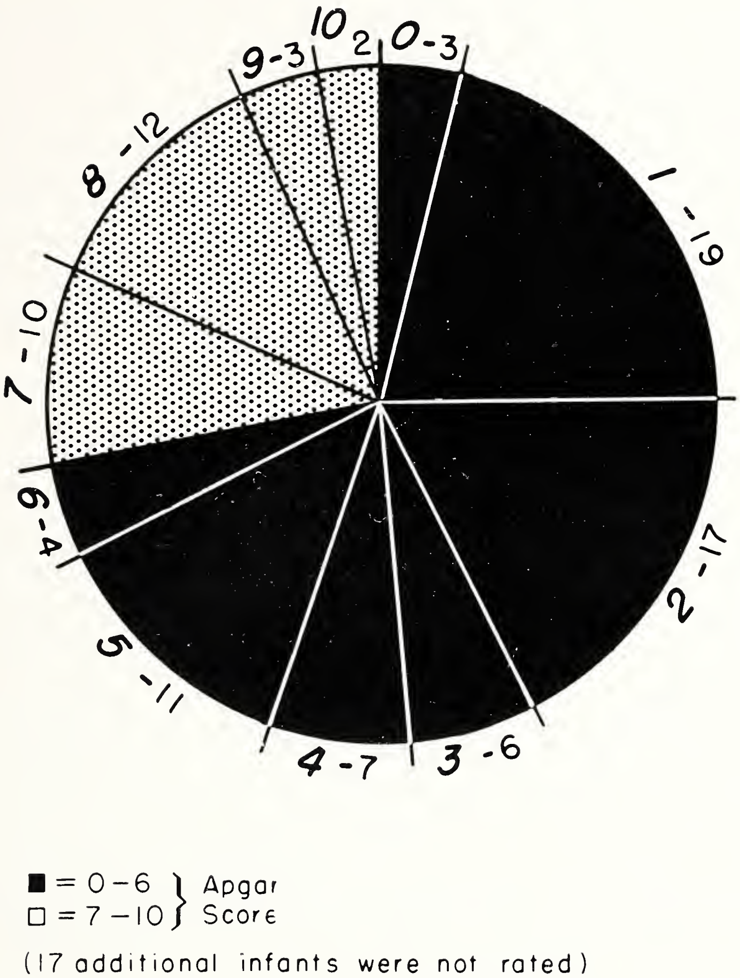

FIGURE 129.—Pie graph showing the relationship of condition at birth, as evaluated by Apgar score, to hyaline membranes in 94 infants weighing from 500 to 2,000 grams. Reprinted, by permission, from James, L. S., and Burnard, E. D.: Biochemical changes occurring during asphyxia at birth and some effects on the heart. In *Ciba Foundation Symposium on Somatic Stability in the Newly Born.* G. E. W. Wolstenholme and M. O'Connor, editors. Boston, Little, Brown and Co., 1961, pp 75–91.

terms of pO_2 in umbilical artery blood. But that isn't a very good way to know at a given moment how asphyxiated the baby might have been and I am not sure that the Apgar score is a good way either. We had more babies who had a low Apgar score at 1 minute among those who later developed hyaline-membrane disease than among an equal group of infants of diabetic mothers who did not. The association of hyaline-membrane disease with a low score is quite definite [12] but not 100 percent, and Dr. James doesn't say it is 100 percent.

JAMES. The ability of the infant to establish and maintain good ventilation and achieve a relatively normal acid-base balance in a short period of time is also important. The very small premature baby who is born in relatively good condition but who is unable to establish normal ventilation and maintain a normal acid-base balance, will rapidly deteriorate. Some of the premature monkeys we studied had almost no oxygen consumption for as long as 5 minutes after birth, despite deep gasping and respectable tidal volumes. Under these circumstances the animals became asphyxiated after birth.

AVERY. Why do you think they got the postnatal asphyxia?

JAMES. I think that some of these very small animals had difficulty in expanding their lungs.

AVERY. Because they lacked something that would make them more compliant, like a surface-active material?

JAMES. That could be, but I don't think so. These lungs appeared to be expanding from the volume recording. We have considered the low initial oxygen consumption to be due to persistence of fetal shunts and a high pulmonary vascular resistance. If one ventilated them for a period of time, their oxygen consumption rose and they were able to maintain themselves for a time.

SEGAL. I think there is one problem of respiratory adaptation that should be included in this conference—one that is frequently seen in the small premature infant who is known to provide a great proportion of the cases of cerebral palsy. Apneic episodes, which are quite characteristic of these infants during their first few days, may cause biochemical insults resembling those produced by asphyxia, particularly if the episodes are prolonged. Perhaps the histological changes which Windle [13] has described in experimental neonatal asphyxia have a bearing on a possible relationship between these prolonged apneic episodes and some of the cerebral palsy seen in this small-weight group.

LEVINE. It is known, isn't it, that there are certain enzyme systems that develop shortly before birth, at birth, or shortly after birth? Dr. Clements told us that surfactant was a saturated choline derivative. Is it possible to take the mouse, for example, and do perfusion experiments at different ages in fetal life and in the mature mouse to study enzyme development?

CLEMENT. I hope it would be possible, Dr. Levine, in appropriate experimental circumstances. The closest approach we have at this moment is to study, in a preliminary way, the lipid composition of fetal lungs at about the time when Dr. Avery has shown surface-active material appearing. We have shown that during this interval the amount of saturated choline-containing phosphatides (which seem to be essential in normal pulmonary surfactant) is increasing, not only in concentration in the tissue but also in proportion to other lipids which can prevent the manifestation of surface activity *in vitro.* The fatty acid composition is simultaneously changing, so that the surface activity of the phosphatides is enhanced while the inhibitory potency of other lipids is reduced. The result of these trends is such that the lungs might develop surface activity rather suddenly in late fetal life without there necessarily being an abrupt appearance of surfactant.

Dr. Levine's question raises other interesting questions, such as what might make certain enzymes appear in greater or lesser amounts in different circumstances, what are the possible genetic factors, and a great many others.

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Editors' Summary

I think the goals we set for ourselves at the onset have been accomplished. Current beliefs of events relating directly or indirectly to neonatal respiratory adaptation have been presented; at the same time, we have learned of the need to greatly broaden our knowledge of these events. We have, in short, asked more questions than we have answered.

Dr. Ramsey has demonstrated the variability with which contrast material is distributed in the uterus from one contraction to the next. It also seems clear that the distribution depends to some extent upon when, in the contraction cycle, the material is injected. These, as well as Dr. Caldeyro's elegant studies of myometrial and amniotic pressures in conjunction with fetal heart rates, point out the need to know much more than we now do about blood flow through the uterus and placenta. Similarly, little is known about blood flow in the fetus. Dr. Barron's data with chronically implanted catheters in the fetal (and maternal) vessels suggest that existing concepts of fetal blood gas values and fetal blood flow may need revision. A critical need has arisen to know about the distribution of blood flow in the fetus. The concept that distribution of blood *away* from the lungs either *in utero* or in the early neonatal period may be a central issue in the pathogenesis of the neonatal respiratory distress syndrome seems to be an important one and certainly needs further study.

We have learned much about the morphological development of the lung and of the possible relationship of the alveolar macrophage to the production of surfactant. But what influences the production of surfactant? Are there inhibitors? Are there enzymatic defects limiting its production which might account for the increased incidence of the respiratory distress syndrome in premature infants?

The conference has also served the function of asking many questions about the neonate. Why does he take the first and subsequent breaths? In short, what controls respiration? How do oxygen lack, carbon dioxide excess, and lowered pH affect blood flow and its distribution not only to the lungs but to other organs as well? Can this flow be modified by pharmacologic agents?

Much more needs to be known about temperature regulation in the neonatal period. What are the critical environmental conditions for the premature and term baby? What is the effect of brown fat on thermogenesis? How does oxygen lack affect thermogenesis? What is the role of norepinephrine?

These are but a few of the questions that have occurred to me during this conference. You doubtless have many more and hopefully will have answered some of them by the time the proceedings are published. But, happily, by then there will be new questions.

THOMAS K. OLIVER, JR., M.D.,
Scientific Editor.

WANDA M. BURNETT,
Technical Editor.

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